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OESOPHAGEAL CANCER SURGERY – NUTRITIONAL DETERMINANTS OF SURVIVORSHIP

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OESOPHAGEAL CANCER SURGERY- NUTRITIONAL DETERMINANTS OF SURVIVORSHIP
THESIS FOR DOCTORAL DEGREE (Ph.D.)

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“He who cannot take part in the friendly meal is half cut off from the society of man.”

- N.A. Myers

1 ABSTRACT

Oesophagectomy, the surgery offered as a curative treatment for cancer of the oesophagus is highly invasive with a radical change in anatomy and carries a risk for significant morbidity and mortality. The recovery is lengthy, burdened by deterioration in health-related quality of life (HRQOL). Eating difficulties and symptoms affecting patients' nutritional status, termed nutrition impact symptoms (NIS) are commonly reported in the survivorship even up to 10 years after surgery. Clinically noticeable weight loss is a problem right from diagnosis but also persists after surgery as a troublesome trait of the survivorship. Hence, this thesis aimed to clarify how nutritional problems after surgery for oesophageal cancer influence HRQOL and survival, and to assess the role of dietitian support in improving nutritional status and thereby contribute to the clinical decision-making process.

Studies I-IV included in this thesis are prospective cohort studies in design based on two large cohorts comprising of patients who underwent surgery for oesophageal cancer in Sweden. **Studies I and II** were based on a prospective cohort including patients operated between 2001 and 2005 and followed up for HRQOL and nutritional outcomes until 2015. **Studies III and IV** were based on a cohort of patients who underwent surgery from 2013 and 2016 and followed up for one and half years after surgery. Clinical variables obtained from medical charts of patients included in both the cohorts provided the possibility to adjust for potential confounders.

In **Study I**, the interactive influence of eating difficulties and weight loss on HRQOL up to 10 years after oesophagectomy were assessed. Severe eating difficulties irrespective of the degree of weight loss were associated with clinically and significantly worse HRQOL in almost all aspects up to 10 years after surgery. **Study II** examined the combined effect of NIS and weight loss on specific HRQOL aspects at six months after surgery and five-year overall survival, stratified by preoperative body mass index (BMI). Patients with severe NIS, regardless of preoperative BMI status and extent of postoperative weight loss, exhibited worse HRQOL. Patients with a higher preoperative BMI and postoperative weight loss, showed worse survival when they experienced severe NIS after surgery. **Study III** investigated the impact of symptoms of early and late dumping syndrome at one year after surgery for oesophageal cancer on specific HRQOL aspects. Clinically and statistically relevant differences in several HRQOL aspects were seen in both early and late dumping when compared with no dumping, with late dumping showing worse effects. **Study IV** evaluated if preoperative dietitian support in addition to postoperative support and a high level of patient reported satisfaction of the support are associated with an improved nutritional status. No differences in nutritional status existed with respect to whether dietitian support was initiated preoperatively or postoperatively and with regards to the level of satisfaction of the support as reported by patients.

In conclusion, symptoms that affect eating and in turn nutrition, experienced after surgery for oesophageal cancer are important determinants of HRQOL. In those who are overweight or

obese before surgery the presence of severe nutritional problems after surgery adversely impacted survival. Patients with symptoms of dumping syndrome, especially late dumping have poorer HRQOL and need attention. Preoperative dietitian support and high level of patient satisfaction of the support did not determine the nutritional status but are integral components of nutritional status.

2 LIST OF SCIENTIFIC PAPERS

I. Anandavadivelan P, Wikman A, Johar A, Lagergren P.
Impact of weight loss and eating difficulties on health-related quality of life up to 10 years after oesophagectomy for cancer.
British Journal of Surgery; 2018;105(4):410-8.

II. Anandavadivelan P, Martin L, Djarv T, Johar A, Lagergren P.
Nutrition impact symptoms are prognostic of quality of life and mortality after surgery for oesophageal cancer.
Cancers; 2018; 10(9).

III. Anandavadivelan P, Wikman A, Mälberg K, Martin L, Rosenlund H, Rueb C, Johar A, Lagergren P.
Prevalence and severity of symptoms of dumping syndrome and their association with health-related quality of life following surgery for oesophageal cancer.
Manuscript.

IV. Anandavadivelan P, Wikman A, Mälberg K, Rosenlund H, Johar A, Lagergren P.
Role of dietitian support in improving nutritional status after oesophageal cancer surgery.
Manuscript.

3 CONTENTS

4 LIST OF ABBREVIATIONS

ANOVA	Analysis of Variance
ANCOVA	Analysis of Covariance
BMI	Body mass index
CI	Confidence interval
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30
EORTC QLQ-OES18	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Oesophagus 18
HR	Hazard ratio
HRQOL	Health-related quality of life
MD	Mean difference
NIS	Nutrition impact symptoms
OSCAR	Oesophageal Surgery in Cancer patients: Adaptation and Recovery
PG-SGA	Patient Generated – Subjective Global Assessment
PG-SGA SF	PG-SGA Short form
PROMs	Patient reported outcome measures
QOL	Quality of life

“Cancer Survivorship is living with, through and beyond a diagnosis of cancer”.

- Dedicated to all cancer survivors

5 INTRODUCTION

Oesophageal cancer is the 11th most common cancer and 6th most common cause of death from cancer globally (1). Worldwide in 2015, approximately 483,000 new cases were diagnosed, and 439,000 deaths were reported (1). In Europe, the United Kingdom has the highest incidence with 9,211 cases diagnosed in 2015 (2). In Sweden, 487 cases were diagnosed in 2016 (3). Oesophageal cancer is a disease with poor prognosis mainly owing to its silent nature with no onset of specific symptoms until it has already advanced (4). Thus merely one third of those diagnosed are eligible for curatively intended treatment (5). Recently, neoadjuvant therapy followed by surgery has shown superior survival benefits than surgery alone. However, surgery remains the mainstay for curative treatment. The surgery by itself is extremely invasive and there is substantial postoperative complications and mortality. The five-year relative survival is as low as 12% in Europe (4). The surgery results in a permanently altered anatomy and patients are thus faced with a challenging postoperative recovery (6).

The survivorship is challenging for four main reasons; 1) decline in health-related quality of life (HRQOL), 2) persisting eating difficulties, 3) malnutrition and, 4) poor long-term survival (6). The worsening of HRQOL is long-lasting up to 10 years after surgery in all aspects, but the worst problems are eating difficulties, reflux and appetite loss (7). Weight loss, a clinical indicator of malnutrition is a central problem faced by patients after surgery. One fifth of patients who undergo surgical resection lose >20% of their preoperative weight in the first six months after operation (8). The surgery leads to changes in the gastrointestinal tract. The subsequent symptoms arising from the anatomical changes are risk factors for long-term severe weight loss of more than 15% (9). These symptoms that impact oral intake and nutrition are collectively referred to as nutrition impact symptoms (NIS). The missing reservoir function is usually accompanied by dumping syndrome, a condition wherein ingested food bypass the stomach rapidly to the intestine (10). The consequent symptoms manifest immediately after or a few hours following ingestion of a meal and classified accordingly as early and late dumping. Also, the pathophysiology of early and late dumping syndrome is distinct to each other.

Although eating difficulties, NIS and malnutrition on the one hand and poor HRQOL on the other hand are recognized problems in the survivorship, it is not clear how the former factors influence the latter. There is thus an underlying need to clarify if the worsening in HRQOL after surgery for oesophageal cancer can be explained by the eating difficulties, NIS and malnutrition and symptoms of dumping syndrome which was the aim of **Study I, Study II and Study III** respectively in this thesis.

Health care support, especially dietitian support is indispensable to help tackle the eating difficulties, NIS and malnutrition better (11). Patients diagnosed with oesophageal cancer, represent a group with a known incidence of malnutrition before and after the surgery (12). Thus, support from dietitians both preoperative and postoperatively seems important with a goal of achieving long-term improvement in nutritional status. Thus, there is a resounding need to clarify if preoperative dietitian support in addition to the postoperative support from dietitians can result in improved nutritional status compared to postoperative support alone that was the aim of **Study IV**. Moreover, behavior modification may prove to be an important goal in the management of eating problems and NIS and patient satisfaction with the dietitian support can be regarded a motivator of behavior modification (13, 14). It is crucial to clarify whether a high level of satisfaction reported by patients is associated with better nutritional status compared to a low level of patient satisfaction of the dietitian support which was another aim of **Study IV**.

6 BACKGROUND

6.1 OESOPHAGEAL CANCER

6.1.1 Anatomy of the oesophagus

The oesophagus, commonly known as the food pipe, is an integral part of the digestive system. The oesophagus is a hollow and muscular tube, approximately 18-26 cm in length. It comprises of several layers of muscle including skeletal muscles and smooth muscles. Its main function is passage of liquids and food from the mouth to the stomach by peristalsis, a wave like motion of the food. Between the oral cavity and the oesophagus is the upper oesophageal sphincter, likewise between the oesophagus and the stomach is the lower oesophageal sphincter. The two sphincters are there to make sure that the food flows in one direction. The lower oesophageal sphincter passes through the diaphragm (Figure 1). The oesophagus is thus in very close proximity to several vital organs in the thorax including the lungs and heart and this anatomical placement complicates surgery in this region with higher risk for complications. The absence of a serosal coating unlike the remaining parts of the gastrointestinal tract aids the spread of tumour cells and also poses a challenge during the surgical procedure of creating an anastomosis after its resection.

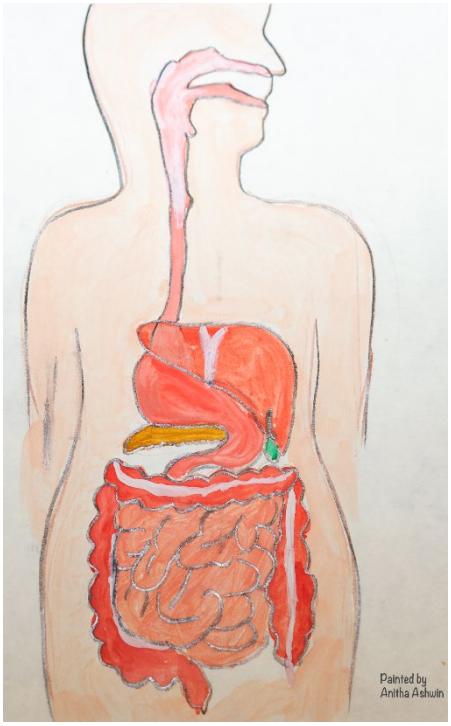

Figure 1. Anatomy of the oesophagus and the bowel.

6.1.2 Incidence and risk factors according to histological subtypes

The global incidence of oesophageal cancer was estimated to be 483,000 newly diagnosed cases in 2015 (1). This is the combined incidence of the two broad histological types of oesophageal cancer namely, squamous cell carcinoma and adenocarcinoma (15). However, these differ substantially in their incidence patterns, risk factors and pathophysiology.

The reported global incidence for squamous cell carcinoma alone was about 398,000 cases in 2012 (16). Higher incidence of squamous cell carcinoma particularly prevails in East Africa, South America and the so called oesophageal cancer belt starting from Northern China through Central Asia to Northern Iran (17). Thus, squamous cell carcinoma encompasses almost 90% of all reported cases of oesophageal cancer making it the most common subtype worldwide. However, the incidence of squamous cell carcinoma is decreasing in several parts of the world (17). The established risk factors for squamous cell carcinoma are tobacco smoking and high intake of alcohol (18). Other factors such as consumption of hot beverages (19), pickled vegetables (20), and exposure to heavy metals (21) are also linked to increased risk for this subtype of oesophageal cancer. Squamous cell carcinoma can affect any part of the oesophagus but usually is in the upper and middle third of the oesophagus (17).

The global incidence of adenocarcinoma in 2012 was about 52,000 cases for adenocarcinoma (16). Although squamous cell carcinoma prevails as the dominant sub-type globally, the incidence of adenocarcinoma surpassed that of squamous cell carcinoma and also other cancer types in many western countries mainly in Northern and Western Europe, North America and Oceania (15, 16, 22). In Europe, the highest incidence was observed in the UK with 9,211 cases in 2016 (2). In Sweden, 487 new cases were detected in 2016 (3). The two well known risk factors for adenocarcinoma are gastro-oesophageal reflux (23, 24) and obesity (25, 26). Reflux and obesity, particularly central obesity seemingly have a synergistic effect that may be created by the raised intra-abdominal pressure in those with higher visceral fat (17). Barrett's oesophagus, a condition wherein cells of the epithelium undergo structural changes arising from ongoing damage from gastro-oesophageal reflux is recognised as a risk factor in the pathogenic pathway of oesophageal adenocarcinoma (27). Thereby, adenocarcinoma always occurs in the lower part of the oesophagus that is subject to prolonged acidic damage from reflux (6). On the contrary, Helicobacter pylori infection of the gastric mucosa is a protective factor (28, 29). The reduction in acidity and gastric juice volume and in turn the risk for gastro-oesophageal reflux may be the biological mechanism linked to this inverse association. Higher consumption of fruits and vegetables, are associated with a protective effect on oesophageal adenocarcinoma (30). Tobacco smoking has a moderate risk, possibly owing to the accentuated gastro-oesophageal reflux among tobacco smokers (31). Genetic predisposition may as well be one of the factors for the causal mechanism of oesophageal adenocarcinoma (15, 17).

Another distinctive factor about the incidence of oesophageal cancer is its striking higher incidence among males. In both histological subtypes, males are affected to a larger extent, with a male to female ratio of 2.4:1 worldwide (22). This ratio is even further increased in the

case of adenocarcinoma with a male to female ratio of between 3 to 9:1 globally (32). The global male to female ratio for squamous cell carcinoma on the other hand is 3:1 (16). The higher incidence of squamous cell carcinoma in males may be explained to an extent by differences in exposures to risk factors such as tobacco smoking and high alcohol intake between the sexes (33). Abdominal obesity that is more prevalent in men than in women seems to partly explain the higher male to female ratio among the adenocarcinoma subtype (34).

6.1.3 Clinical presentation

Late onset of symptoms is a major reason for concern in oesophageal cancer. Symptoms do not manifest early on owing to the elastic nature of the oesophagus that allows the tumour to grow silently often to an advanced stage until it has already started to spread. The first symptoms that are noticed by patients are usually difficulty swallowing (i.e., dysphagia), pain while swallowing (i.e., odynophagia) and involuntary weight loss (15, 17). Dysphagia early on is mild, presented as discomfort and occasional pain when swallowing. As much as 74% of patients with oesophageal cancer report dysphagia as a common symptom at diagnosis and 17% report odynophagia (35). The dysphagia may be related to vomiting from undigested food as a result of oesophageal obstruction when the tumour has grown and has systemically spread (15, 35, 36). Consequently, patients are likely to change their eating habits even before a clinical diagnosis is made, owing to the difficulties in eating solid foods or occasionally even consuming liquids. The mechanical changes resulting from the tumour is thereby a predominant contributor to weight loss that occurs from the onset of the cancer. About 38% of the total estimate of the cause of weight loss in patients with oesophageal cancer is associated to impaired dietary intake at diagnosis (37). Some other symptoms may include hoarseness or cough caused by infringement of the laryngeal nerve by the tumour, occasionally passing of dark stools or vomiting blood due to internal bleeding in the gastrointestinal tract and fatigue as a general symptom of cancer (17). Worsening of symptoms especially dysphagia often lead patients to seek a clinical investigation.

Another trigger for weight loss is the systemic inflammation that arises as a result of the response of the host immune system to the presence of the tumour mediated by pro-inflammatory cytokines (38-40). The cytokines are produced both by host and tumour cells and in turn lead to the release of acute phase reactants such as C-reactive protein (40, 41). Patients with oesophageal cancer who can eat a normal diet with no dysphagia still lose 4.4% of their body weight by the time of diagnosis (37). About 34% of the independent estimate of the cause of the weight loss is attributable to systemic inflammation (37). This inflammatory state leads to increased metabolic demands that are not compensated by adequate oral intake (42). This leads to mobilisation of body protein and/or fat stores leading to weight loss, especially skeletal muscle loss. This loss of skeletal muscle is a hallmark characteristic of weight loss experienced by patients with cancer and is referred to as cancer cachexia (43). Low muscle mass (i.e., $\geq$ 2SD below that of young adults) is termed as sarcopenia and specifically as myopenia, when caused by a chronic disease process (43-45). Most patients

with oesophageal adenocarcinoma are overweight or obese (body mass index [BMI] > 25) at diagnosis. From the onset of the disease, there is ongoing and progressive weight loss in patients with oesophageal adenocarcinoma (46). On the other hand, most patients with squamous cell carcinoma are malnourished even at the time of diagnosis compared to a majority of adenocarcinoma patients who are still overweight/obese at diagnosis (47, 48). Weight loss that corresponds to malnutrition is a decisive factor in the overall treatment of cancer patients because of its major negative impact on treatment, prognosis and quality of life (49). Malnutrition and overweight/obesity have distinct implications and are recognised prognostic factors in cancer (50).

6.1.4 Diagnosis and staging

On clinical presentation an endoscopy is warranted as the primary procedure and considered a gold standard for diagnosis (15, 17). Tumour characteristics such as the length and location are assessed with the endoscopy (17). A confirmed diagnosis is made by means of biopsies taken during the endoscopy to determine the histology of the tumour. Additionally, a computed tomography (CT) of the thorax and abdomen is performed to carry out tumour staging and assess the lymph node involvement and metastasis (51). The stage of the tumour i.e., how far the tumour has grown is determined by means of the TNM classification system. The system takes into consideration the depth of the tumour (T), number of lymph nodes with cancer (N) and distant metastasis (M) or spread of cancer to other parts of the body which are ascertained by gastroscopy with biopsies, CT with contrast and endoscopic ultrasounds. When no distant metastasis is detected by CT, a positron emissions tomography CT (PET-CT) should be considered (52). There are 0-IV major groups for the TNM staging that are commonly used and the current system also takes into account the tumour grade, i.e., differentiation of the tumour cells in comparison to normal cells by a pathologist and the cancer location in relation to distance from the teeth (53).

6.1.5 Treatment with intent to cure

6.1.5.1 Multidisciplinary meeting

A well-coordinated multidisciplinary meeting is required for deciding the optimal course of an individual's treatment involving the consensus of a team of experts including pathologists, surgeons, oncologists, radiologists, dietitians and specialist nurses (15). The stage of the tumour as determined by the TNM system, the physical fitness level of the patient, co-morbidities and patient preferences are important considerations while deciding the treatment plan (54). Besides these, the nutritional status of the patient is an essential factor to be considered as it is related to the prognosis (55). Therefore, assessment of nutrition status and consultation with a dietitian are considered valuable before treatment options are considered (Figure 2). Only one third of those who are diagnosed with oesophageal cancer, without distant metastasis and adequate level of fitness are deemed eligible for curative treatment (5). In Sweden, 30% of patients who were diagnosed with adenocarcinoma underwent surgery

and 24% of patients with squamous cell carcinoma were operated between 1990 and 2013 (56).

Figure 2. Illustration of dietitian support before treatment options for oesophageal cancer are considered.

6.1.5.2 Neoadjuvant therapy

Surgery is the mainstay of curative treatment for oesophageal cancer. However, in the last decade, the use of multimodality approach has been steadily increasing owing to a survival benefit for those who undergo neoadjuvant therapy before surgery compared to surgery alone (57, 58). Thus, the majority of patients selected for curatively intended treatment undergo neoadjuvant chemo radiotherapy followed by surgery (59). Chemotherapy in patients with advanced disease decreases the primary tumour size aiding radical resection, treating micro-metastatic disease and reduce the risk of tumour recurrence (17). However there is substantial weight loss during the course of neoadjuvant therapy for oesophageal cancer (60) that is associated with adverse prognosis on postoperative weight loss (61) and mortality (60). Appetite loss, depression and oesophagitis are identified as risk factors for weight loss during neoadjuvant therapy (62). Malnutrition during neoadjuvant therapy is related to adverse outcomes concerning poor tumour response, poor treatment tolerance, increased neoadjuvant treatment related morbidity, and reduced quality of life (QOL) (63). Thereby during neoadjuvant therapy nutritional optimisation in patients who are malnourished and those who are unable to eat is warranted. Counselling by a dietitian is recommended at the time of diagnosis for evaluating the need for enteral nutrition during neoadjuvant therapy. Enteral feeding routes including jejunostomy, gastrostomy and nasogastric tube feeding are used but no optimum single approach is recognised (64).

6.1.5.3 Surgical approach

The surgery for oesophageal cancer is a highly invasive procedure. It involves the surgical resection of a major part of the oesophagus and/or part of the stomach or the entire stomach depending on where the tumour is located and if it has spread to the gastro-oesophageal junction or stomach. The resection is followed by a surgical reconstruction of the stomach into a tube that is pulled up and attached to the thorax or neck (Figure 3). There are two principal approaches – the transthoracic, that includes access through the chest wall, or transhiatal surgery, where thorax is not accessed through the chest wall (15). Transthoracic oesophagectomy can further be done using one left-side thoracoabdominal incision (the Sweet oesophagectomy), incisions in the abdomen and right chest (Ivor-Lewis oesophagectomy) and three incisions similar to Ivor-Lewis and adding a neck incision (the McKeown oesophagectomy). The choice of approach depends on tumour location, total lymph nodes to be removed, access to lymph nodes and the experience of the surgical team (32). The survival does not seem to differ significantly between the transthoracic and transhiatal approaches (65). In the recent years, minimally invasive oesophagectomy has come to evolve as a favourable and safe surgical technique for oesophagectomy and is the main surgical approach in many countries (66). The procedure can be performed as a hybrid procedure combining laparoscopy with open thoracotomy, or thoracoscopy with open laparotomy or completely minimally invasive procedures, following the

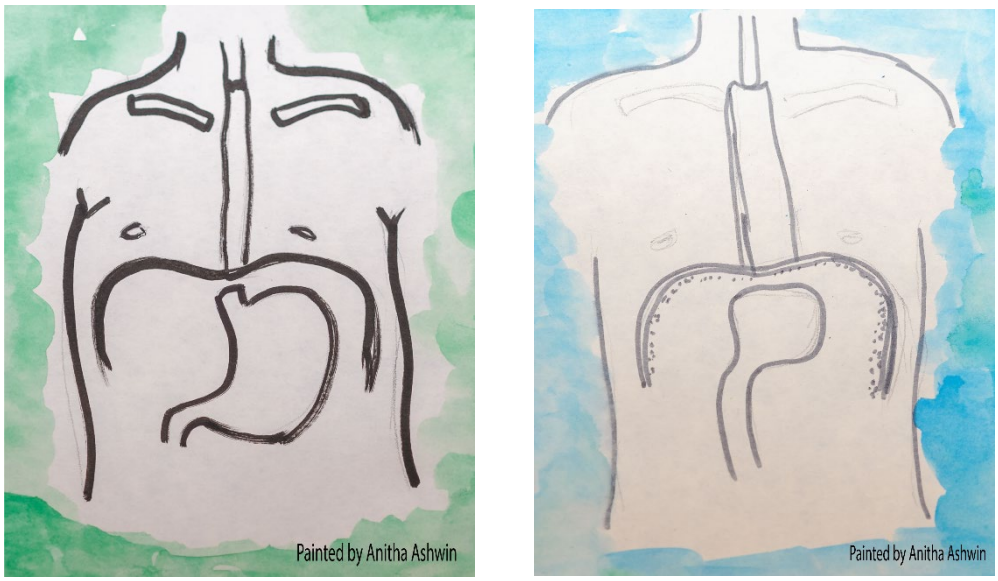

Figure 3. Illustration of the oesophagus and stomach (left) and replacement of the oesophagus with a gastric substitute (right).

steps of transhiatal or transthoracic oesophagectomy (17). Minimally invasive surgeries are associated with lesser perioperative blood loss, reduced rate of pulmonary infections and shorter hospital stay, improved postoperative QOL, without any clear significant disadvantages including survival compared to an open surgery (67, 68). Also, the wound trauma with the extensive invasion that is required for oesophagectomy is significantly reduced. However, open oesophagectomy remains an alternative during emergency situations or if an alternative reconstruction method is warranted, such as when colon interposition is used. Thus minimally invasive surgeries have not and may not completely replace open surgeries.

6.1.6 Postoperative complications

Patients undergoing oesophagectomy frequently get complications, which can result in poor oncological outcomes as well as poor HRQOL. Postoperative complications ranging from 30% to 50% are reported in the literature (69, 70). A comprehensive review on oesophagectomies performed in high volume centers reports an overall complication rate of 59% and a Clavien Dindo severity grade of IIIb or higher among 17.2% (71). However, it is noteworthy that these are related to open surgeries.

Among surgical complications, anastomotic leakage is regarded as the most devastating and is associated with worse short-term and long-term survival and recurrence (72, 73). Medical complications are more common than surgical complications. The most common ones are pulmonary complications and respiratory failure and are associated to greater mortality (74, 75). Some clinical trials show an increased risk of pulmonary complications following a transthoracic approach compared with use of the transhiatal approach (65) and minimally invasive surgery (76). Minimally invasive surgery is associated with lesser pulmonary complications and lesser morbidity than open oesophagectomy (77). Also, preoperative poor nutritional status assessed based on serum albumin, cholesterol, and total lymphocyte count is associated with worse postoperative complications (55).

The Enhanced Recovery After Surgery (ERAS) guidelines and program are designed to reduce postoperative morbidity and improve postoperative recovery after oesophagectomy in various surgical settings (78). Following this, many oesophageal cancer centers have launched Enhanced Recovery program (ERP) in the recent years for improving postoperative outcomes (79). The ERP is based on the ERAS approach that developed in 2001 mainly for colorectal surgery and the ERAS society was formed in 2010 to consolidate and promote ERAS principles for all surgery types (80). The ERAS is a multimodal approach to maximize efficiency during surgery by enhancing perioperative care with the best available evidence to achieve early recovery for patients undergoing major surgery. The ERP implemented for oesophageal cancer shows improved length of hospital stay (81).

6.1.7 Survival

Oesophageal cancer is a disease with an overall poor survival. There are disparities in the survival rates between geographic regions. In Europe, USA and China, 10-22% of patients survive five years from diagnosis. The overall survival rates in Europe have been improving in patients with oesophageal cancer but still remains lower than 15% (22), while the one-year and five-year relative survival are 40% and 12% respectively (4). The population-based five-year survival rate following resection for oesophageal cancer has been reported to be 30% to 55% with noticeable improvement in the last few years (82, 83). A risk of >5% for in-hospital mortality exists (69). The relative five-year survival has improved for squamous cell carcinoma (9% to 12%) and adenocarcinoma (12% to 15%) in Sweden in the last two decades (84). The corresponding survival rates in those who underwent surgery increased from 24% to 43% in those with squamous cell carcinoma and 27% to 45% in adenocarcinoma. High surgeon and hospital volume are factors associated with better survival in oesophageal cancer (85-87) and justifies why the treatment of oesophageal cancer have been centralised. The improving survival trends may thus be attributable to the improving awareness, diagnostics, multimodality treatment and centralisation of surgery in Sweden (84). On the other hand, tumour recurrence is the main contributor to worse prognosis after surgery. More than half the patients who are operated with curative intent develop a tumour recurrence (17). Most tumour recurrences and deaths occur early after treatment, while those who survive for three years following diagnosis are usually considered cured as late recurrences are very rare (15, 88).

6.1.8 Palliative treatment

About the 76% of patients who are diagnosed with oesophageal cancer undergo palliative care in Sweden (89). Patients who have tumours with local overgrowth into adjacent tissues or organs or with distant metastases are usually not eligible for curatively intended treatment (15). The aim of palliative therapy is to improve HRQOL by minimising cancer related symptoms and prolong survival (6). Dysphagia is a predominant cause of distress and stenting with brachytherapy may be an optimal treatment option to relieve dysphagia (90). Chemotherapy prolongs survival moderately compared to only best supportive care however the treatment related effects can be burdening. Malnutrition is severe and support with nutrition during chemotherapy and radiotherapy is an important goal to maximise patient comfort and HRQOL. Enteral nutrition with percutaneous endoscopic gastrostomy seems to be a preferable route especially when food intake is intolerable owing to mucositis from radiotherapy to avoid conduit related damage and avoid further complications (91).

6.2 HEALTH-RELATED QUALITY OF LIFE

6.2.1 Cancer survivorship

Cancer survivorship is the experience of living with, through and beyond a diagnosis of cancer and described in three phases 1) Acute survival – is the treatment phase from the time of diagnosis and initial therapy, 2) Extended survival – period of watchful waiting and uncertainty of recurrence and the future, 3) Permanent survival – experience less fear and an increasing sense of permanency (92). With the introduction of the term survivorship by Dr Mullan in 1985, the term survivor has changed to encompass anyone from the diagnosis of cancer onwards. Ever since, there has been increased emphasis on HRQOL as an important outcome in cancer survivorship.

6.2.2 The concept of health-related quality of life

Quality of life is a concept known in many fields and defined depending on the area in which it is used. When used within the framework of diseases and their treatment, it is referred to as "health-related quality of life" and is more relevant for use in clinical or research settings (93). There is no single agreed upon definition of HRQOL. Most definitions however are unanimous in agreeing that HRQOL is a subjective experience reported from the patient's perspective (94-96). The concept of HRQOL has however evolved to be much broader since the definition of health as a state of complete physical, mental and social well-being and not just the absence of disease was established by the World Health Organization in 1946 (97). Thus HRQOL is recognized more as a multi-dimensional concept that includes aspects such as physical function, emotional function, social function and physical symptoms (93).

6.2.3 Measuring health-related quality of life

The Food and Drug Administration in the United States introduced the term Patient Reported Outcomes (PROs) to reiterate the subjective characteristic of HRQOL measures (98). It is defined as 'a measurement that comes directly from the patient about the status of a patient's health condition without amendment or interpretation of the patients response by a clinician or anyone else' (98). It is often interchangeably used with Patient Reported Outcome Measures (PROMs). Questionnaires are the principal PROMs to assess HRQOL. There are multiple questionnaires available with different purposes but they can be broadly divided into three categories: A) Generic questionnaires - used across any population to compare within or between different populations irrespective of the condition or disease being studied, e.g. the Medical Outcome Study Short Form-36 (99), B) Disease specific questionnaires - used to assess HRQOL in patient with a specific disease, e.g. the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 (100) or Functional Assessment of Cancer Therapy – General (FACT-G) (101) used in patients with cancer. Disease specific questionnaires can be supplemented with site-specific modules depending on the cancer site e.g. EORTC QLQ-OES18 (102) or FACT-E developed to measure oesophageal cancer specific symptoms, C) Aspect specific questionnaires – are instruments used to assess specific aspects

influencing QOL e.g. the Hospital Anxiety and Depression Scale (HADS) which measures anxiety and depression (103) and McGill Pain Questionnaire (MPQ) which measures pain (104).

6.2.4 Psychometric properties of PROMs

Besides the type of aspects, the suitability of the instrument based on factors such as endpoint (primary/secondary), study population, intended frequency (how often used in study), participant burden (time to fill the questionnaire) and handling missing data from the responses should be considered in choosing a questionnaire for use in clinical research (105). A suitable HRQOL questionnaire should therefore exhibit psychometric properties i.e., it should satisfy basic properties namely, validity, reliability, sensitivity and responsiveness (96, 106, 107). Validity describes the degree to which an instrument measures what it is intended to measure and is also referred to as accuracy (108). Reliability concern the random variability in measurements and if the instrument measures what it is supposed to when used repeatedly. They are often referred to as reproducibility or precision. Sensitivity describes whether an instrument can capture differences between patients or between groups and responsiveness is the ability to detect changes over time (109). While measuring HRQOL over time another factor to be considered is response shift, a change in the meaning of an individual's self-evaluation. Response shift was initially defined based on two concepts, recalibration, a change in the internal standard of measurement and reconceptualisation, a redefinition of the target constructs. Later, the concept of reprioritisation i.e., change in values was added to its definition by Sprangers and Schwartz, who explain response shift in HRQOL outcomes owing to a change in an individual's health status with a conceptual model. The change in health status acts as a catalyst that triggers an adaptation mechanism by means of behaviour, cognitive or affective processes. The processes in turn act in liaison with the personality or gender of the individual and may lead to change in perceived HRQOL, causing the response shift. Adapting to a major event such as a cancer diagnosis and treatment is considered to create a response shift as in the model and this may have an implication on interpreting meaningful differences in scores. The then test is a widely used approach to assess response shift. There is still a lack of studies that have explored response shift in patients with oesophageal cancer.

6.2.5 Patient reported outcome measures in oesophageal cancer survivorship

Several PROMs are used to measure HRQOL in patients with oesophageal cancer. A meta-analysis, shows that among 58 studies, 11 different PROMs are used to assess HRQOL after oesophagectomy (110). A generic questionnaire with the addition of a disease-specific questionnaire are most commonly used across the studies. The EORTC QLQ-C30 along with the oesophageal cancer specific module QLQ-OES18 are the most commonly used questionnaires and were recommended with regards to reproducibility (110).

The EORTC is an international non-profit organisation founded in 1962 with the aim to conduct, develop, coordinate and stimulate cancer research in Europe (111). A quality of life group from the EORTC led the development of the EORTC QLQ-C30 from a core version (EORTC QLQ-C36) to its current version EORTC QLQ-C30 version 3.0 (100). It is an integrated and multidimensional tool for assessment of HRQOL in cancer survivors in research settings where PROMs are collected. It is designed to be used across a wide range of populations of patients with cancer as a disease specific questionnaire. The current standard version EORTC QLQ-C30 3.0 has nine multi-item scales including five functional scales (physical, role, cognitive, emotional, social), three symptom scales (fatigue, pain, and nausea and vomiting), one global QOL scale and six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties) (111). The psychometric properties of the QLQ-C30 have been investigated extensively and is recommended as a well-validated tool for assessing HRQOL in patients with cancer (100, 112-115). The first version of the EORTC QLQ-C30 is tested in a cross-cultural population of lung cancer patients in 13 countries and demonstrated good reliability and validity (100). The latest version 3.0 is tested in a study with head and neck cancer patients from 12 different countries and exhibited good psychometric properties (115).

In addition to the generic questionnaire, the disease specific original module QLQ-OES24 was developed by EORTC to assess symptoms and QOL issues that are specific to oesophageal cancer (102). The psychometric validation of QLQ-OES24 resulted in the refined module QLQ-OES18 (116). It consists of four symptom scales (eating, reflux, oesophageal pain and dysphagia) and six single items (cough, dry mouth, taste, choking, speech and trouble swallowing saliva). The psychometric properties of the questionnaire were tested and showed well defined distinguishment between clinically distinct groups and had good clinical validity (116).

The responses for all scales and single items on the QLQ-C30 and QLQ-OES18 are assessed on a four-point Likert scale: 1 - Not at all; 2 - A little; 3 - Quite A Bit; 4 - Very much, except for the global QOL scale on the QLQ-C30 which is measured on a scale ranging from 1-7, where 1 being the lowest score (very poor) and 7 the highest (excellent). The respondents are instructed to pick the number that applies best to them. The raw scores from the responses are calculated and then transformed to a scale of 0-100 points according to instructions from the EORTC scoring manual (111). A higher score on the global QOL scale and functional scales indicates better function while on a symptom scale or single item a higher score means worse symptoms.

6.2.6 Health-related quality of life after oesophagectomy

In the short-term (six months) following surgery for oesophageal cancer, HRQOL outcomes deteriorate substantially (117-124). In a meta-analysis, symptoms such as fatigue, dyspnoea and diarrhoea are worse at six months while emotional function showed improvement (125). Building on this another meta-analysis demonstrates clinically relevant and long-lasting deterioration in HRQOL after oesophageal cancer surgery in several HRQOL aspects, including social functioning, role functioning, and increased symptoms of fatigue, pain, cough, dry mouth, and reflux up to one year after surgery (126).

In the longer term, while some studies have shown an improvement in specific aspects of HRQOL in long-term survivors up to five years from surgery (120, 127, 128), others demonstrate poor recovery in most aspects among survivors up to five years (119, 120, 129). However, it is important to note that improvement may not mean levels similar to before disease occurrence and is difficult to ascertain owing to the heterogeneity in methodology used in these studies (125). Deterioration in some aspects of HRQOL such as physical function; general and oesophageal cancer specific symptoms remain a reason for concern even long-term following oesophagectomy (119, 125, 130). At five years from surgery, HRQOL deteriorates noticeably in a sub-group of patients while the remaining majority of patients return to levels comparable to the general population (131). A population-based study on 10 year survivors shows that patients who undergo surgery for oesophageal cancer do not recover in HRQOL even at 10 years compared to a reference population, independent of ageing, sex and co-morbidities (7). Taken together, the available evidence shows substantial problems with HRQOL after oesophagectomy for oesophageal cancer both in the short- and long-term that are clinically relevant.

6.2.7 Predictors of health-related quality of life after oesophagectomy

Patient factors such as co-morbidities, younger-age, and low-education level are related to poor postoperative HRQOL (132, 133). An advanced tumour stage, a tumor located in the middle or upper oesophagus and histology of squamous cell carcinoma are tumour-related factors that worsened HRQOL after surgery (134). Neoadjuvant therapy eases dysphagia (135, 136) but affects other aspects of HRQOL during the course of the treatment, however there is improvement in HRQOL before surgery (137). No differences in HRQOL are seen between those who have neoadjuvant therapy before surgery and those who undergo surgery alone (138). No particular surgical factors are identified as adverse predictors of postoperative HRQOL (139, 140). In a meta-analysis, minimally invasive surgery show better HRQOL at 3 months compared to open surgery in some aspects, but the differences between the techniques do not persist at longer follow-up of six and 12 months (141). Postoperative complications affect HRQOL negatively both in the short- and long-term (142).

6.3 POSTOPERATIVE NUTRITIONAL STATUS

6.3.1 Elements of nutritional status

There is no one unanimous definition that prevails for nutritional status, neither is there one set of generally accepted principles for assessing nutritional status in general (143). It is agreed by experts in the field of clinical nutrition that there are three major domains considered important in assessing nutritional status – involuntary weight loss, BMI and reduced nutritional intake although no consensus for their cut-off points have been defined (144).

6.3.2 Weight loss after surgery for oesophageal cancer

The severity of weight loss is a reliable indicator of involuntary weight loss and is best evaluated by assessing the rate of loss and expressed as a percentage of total body weight (43). In a cohort of 226 patients in Sweden, 63.7% and 20.4% lose ≥10% and ≥ 20% of their preoperative body weight at six months postoperatively, respectively (8). In a study from France, among 304 patients, 54% lose ≥ 10% of their initial body weight at six months after surgery (145). In the same study, 55% experience a weight loss ≥ 10% of their preoperative body weight at one year postoperatively. Another study from Korea, shows that among 181 patients, 51.4% lose more than 10% preoperative body weight and 10.5% lose more than 20% of body weight at one year postoperatively (146). However, 96% of the patients are operated for squamous cell carcinoma in this study and can be inferred that most patients face problems with weight loss after surgery irrespective of the histological type. Further assessment of long-term weight status in Sweden shows that 33.8% of 203 patients and 36% of 117 patients lose >15% of their preoperative weight at 3 years and 5 years from the time of oesophagectomy respectively (9, 147). According to the guidelines of the European Society of Parenteral and Enteral Nutrition, patients undergoing oesophagectomy are at severe nutritional risk (148). Clinically significant weight loss is a persisting problem after surgery for oesophageal cancer. The extent of postoperative weight loss emphasises the importance for dietitian support and additional nutritional support postoperatively.

6.3.3 Risk factors for weight loss

Risk factors for malnutrition after surgery for oesophageal cancer are high preoperative BMI, female sex and neoadjuvant therapy (61). A high BMI of ≥25 at diagnosis is associated with increased risk of long-term weight loss and malnutrition after surgery (9, 147). As much as ≥10% weight loss is more prevalent among patients with a high preoperative BMI (≥25) compared to those with normal (20-25) or low (<20) BMI (8). The risk of severe weight loss (≥15%) is consistently more pronounced among patients with a high preoperative BMI (≥25) at 6 months, 3 and 5 years (8, 9, 147). Initial body weight and postoperative vocal cord palsy are risk factors for one year postoperative weight loss (146). It is apparent from the available literature that being overweight or obese before surgery is a risk factor for higher weight loss after surgery making it a very important determinant while assessing malnutrition in this patient group.

6.3.4 Nutrition impact symptoms

Symptoms as a consequence of cancer and its treatment or medical co-morbidities influence patient's nutritional status. A spectrum of symptoms that can interfere with oral nutrition intake or absorption in the gastrointestinal tract and increase the risk for malnutrition are conceptualised as nutrition impact symptoms (NIS) (149). The importance of assessment of NIS in the oncology setting is obvious especially in cancer populations with high incidence of malnutrition to understand their association with clinical outcomes and HRQOL. Several study-specific questionnaires and symptom checklists are used to assess NIS in cancer survivors. The Patient-Generated Subjective Global Assessment (PG-SGA) is a nutrition assessment tool specifically developed for use in the cancer population and commonly used in nutrition studies undertaken in oncology patients (150). The abridged version, the PG-SGA Short form, has also been validated in the oncology setting (151). The NIS component of PG-SGA Short form comprises of 15 common symptoms or impediments that negatively influence food intake, absorption or utilisation of nutrients that are assigned scores based on how likely the symptom affects the nutritional status i.e., (0=low impact on nutritional status; 1=mild; 2=moderate 3=potentially severe). A score ≥ nine reflects a need for nutritional intervention or clinical management (152).

6.3.5 Common nutrition impact symptoms post oesophageal cancer surgery

After surgery for oesophageal cancer, a clear majority of patients have long-lasting and clinically relevant deterioration in symptoms of fatigue, pain, cough, dry mouth, and reflux (126). At six months after surgery, three symptom clusters are identified: fatigue/pain, reflux/cough and eating difficulties (153). Of these clusters reflux/cough and eating difficulties are associated with a higher risk of mortality. Symptoms of fatigue, diarrhoea, appetite loss, nausea and vomiting are worse at three years after surgery (119). Patients who deteriorated in HRQOL over time have worse scores for all symptoms from the QLQ-C30 and QLQ-OES18 at five years from surgery (131). Even at 10 years after surgery patients report symptoms of reflux, eating difficulties, diarrhoea and appetite loss (7). Eating difficulties can be assessed using the eating difficulties scale (comprising of four items on the QLQ-OES18) i.e., trouble enjoying meals, feeling full too quickly, trouble eating, trouble eating in front of others (116). Eating difficulties are risk factors in patients who encounter long-term severe weight loss of >15% (9). A study showed that patients who are operated with an extended transthoracic resection have higher incidence of eating difficulties compared to those with a limited transhiatal approach (154).

6.3.6 Symptoms of dumping syndrome

Following oesophagectomy, several functional and mechanical problems occur often leading to malabsorption (155). The altered anatomy with a missing reservoir function of the stomach causes dumping syndrome, a condition where contents of ingested food bypasses the stomach rapidly similar to an unloading dump truck (Figure 4) (156). Dumping syndrome often is experienced as a constellation of symptoms, that may occur either early (30-60 minutes after

a meal) or late (one-three hours after a meal). The pathophysiology of early and late dumping syndrome is distinctive (157). In early dumping rapid fluid shifts occur from the plasma compartment into the intestinal lumen owing to the hyperosmolality of the food, resulting in hypotension and a sympathetic nervous-system response. While in late dumping there is an incretin-driven hyper insulinemic response after carbohydrate ingestion (157). Some symptom-based questionnaires of dumping syndrome are used to assess symptoms that are suggestive of dumping syndrome e.g., the Sigstad and the Arts questionnaire. However, neither of them has diagnostic validity for dumping syndrome (157). Glycemic measurements of plasma glucose concentrations and provocative tests such as oral glucose tolerance tests and mixed-meal tolerance tests are suggested as diagnostic tests to diagnose

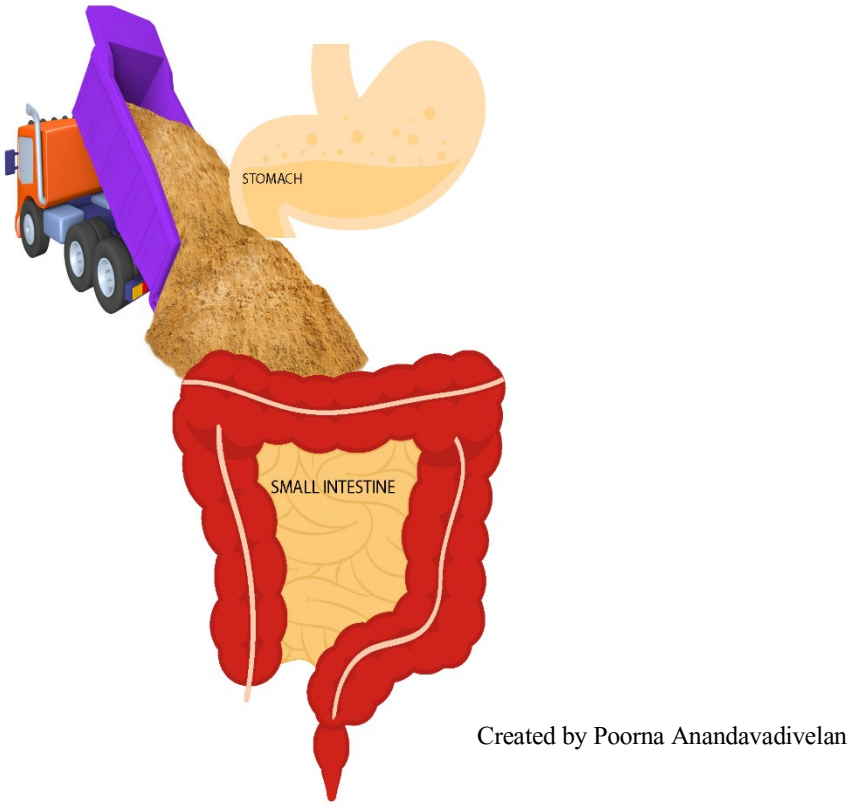

Figure 4. Illustration of an analogy of a dump truck and dumping syndrome.

dumping syndrome but to date no definitive guidelines or optimal approach for their use exists (157). A wide incidence of dumping syndrome ranging from 0-78% following oesophageal resection for cancer are reported in a systematic review (158). Female-sex and younger-age are risk factors for dumping after the surgery (159). The mechanism for dumping syndrome after oesophagectomy may be attributed to a lack of vagal reflexes and the removal of the portioning mechanism of the antrum and pylorus, resulting in premature gastric emptying. However, no particular surgical risk factor has been identified (158).

It is apparent that the majority of patients who undergo surgery for oesophageal cancer are at risk for malnutrition after the surgery. It is also evident that they have impaired HRQOL and poor prognosis after the surgery. There is an underlying need to identify if nutritional problems after surgery for oesophageal cancer can explain the reduced HRQOL to be able to tailor interventions to improve their HRQOL and survival.

7 AIMS

The overall aim of this thesis was to contribute to clinical decision making regarding which nutritional factors influence HRQOL and survival after oesophageal cancer and to identify factors associated with improved nutritional status.

The study specific aims were:

1. To clarify the combined effect of clinically relevant weight loss and eating difficulties on the trajectory of HRQOL up to 10 years after surgery for oesophageal cancer
2. To assess the interactive influence of clinically relevant weight loss and nutrition impact symptoms on short-term HRQOL and long-term survival after surgery for oesophageal cancer
3. To evaluate how symptoms of early and late dumping syndrome affect HRQOL after surgery for oesophageal cancer
4. To elucidate the role of preoperative dietitian support and patient reported satisfaction of the support on nutritional status after surgery for oesophageal cancer

8 MATERIALS AND METHODS

8.1 OVERVIEW

Table 1. Overview of materials and methods used in **Studies I – IV**.

	Study I	**Study II**	**Study III**	**Study IV**
Study design	Prospective population-based cohort study			
Data sources	Swedish Esophageal and Cardia Cancer (SECC) cohort		Oesophageal Surgery on Cancer Patients Adaption and Recovery (OSCAR) cohort	
Study Population	All Swedish residents undergoing curatively intended surgery for oesophageal or cardia cancer			
Inclusion period	2nd April 2001 - 31st Dec 2005	2nd April 2001 - 31st Dec 2005	1st Jan 2013 - 31st Dec 2016	1st Jan 2013 - 31st Dec 2016
Follow-up period	2nd April 2001 – 31st Dec 2015	2nd April 2001 - 31st Dec 2010	1st Jan 2014 - 31st June 2018	1st Jan 2014 - 31st Dec 2017
Dependent variable (exposure)	Weight loss and eating difficulties	Weight loss and NIS	Symptoms of early and late dumping syndrome	Dietitian support
Independent variable (outcome)	HRQOL	HRQOL and five-year overall survival	HRQOL	Nutritional status
Confounders	Age, sex, preoperative BMI, tumour stage, co-morbidities, time	Age, sex, co-morbidities, tumour stage, tumour location, histology, operation type, postoperative complications	Age, sex, co-morbidities, neoadjuvant therapy, tumour stage, tumour histology, surgical approach, postoperative complications, postoperative eating difficulties	Age, sex, co-morbidities, preoperative BMI, neoadjuvant therapy, tumour stage, tumour histology, surgical approach, pre and postoperative enteral/ parenteral nutrition support, postoperative complications, recurrence
Statistical methods	Repeated measures ANOVA model	ANCOVA and Cox proportional hazards model	ANCOVA model	ANCOVA model

8.2 DATA SOURCES

The main data source for **Studies I and II** in this thesis was the Swedish Esophageal and Cardia Cancer (SECC) cohort (23, 160). Additional data sources for **Study I** was the Reference Population study (161) and for **Study II** was the Swedish Causes of Death register (162). **Studies III and IV** are based on the Oesophageal Surgery on Cancer Patients Adaption and Recovery (OSCAR) cohort.

8.2.1 The Swedish Esophageal and Cardia Cancer (SECC) cohort

The SECC is a nationwide cohort comprising of almost all patients who underwent curatively intended surgery for oesophageal or gastro-oesophageal junctional cancer from April 2001 to December 2005 in Sweden. The cohort was assembled based on an extensive network of contact physicians at hospitals treating oesophageal and cardia cancer patients and collaboration with the six regional cancer centers in Sweden (23). Of 179 hospitals, 174 (97%) participated in the study. In total 616 patients (90% of all operated) were included in the cohort until the end of the study period. The SECC cohort was approved by the Regional Ethical Review Board in Stockholm (DNR 01-064, with amendments 01-340, 05/1491-32 and 2012/712-32). An informed written consent was obtained from all patients before inclusion.

The overview of the data collection in SECC is shown in Figure 5. A centrally administered data collection by a single study coordinator with regular reminders to the contact physicians at the participating hospitals ensured high quality, thorough coverage in patient inclusion and completeness in the medical records retrieved. The collaboration with the six regional cancer centers ensured better control over all operable oesophageal cancer cases enabling a close to full national coverage. The 10% non-participation was mainly owing to the five non-participating hospitals (23). The obtained medical charts were scrutinized by a team of researchers who were also clinicians using a detailed and pre-defined study protocol. The study protocol was developed by experienced oesophageal cancer surgeons and researchers, which ensured a meticulous data collection of clinical variables regarding co-morbidities, tumour characteristics, operation, length of stay in hospital, postoperative complications. Also, the data being obtained by personnel not directly involved in the treatment of the patients increased the validity. Well-validated questionnaires were used for the HQQOL data obtained at the four follow-up time points, six months, three, five and ten years. The 15-year follow-up is ongoing. Up to three reminders were sent if required, for unreturned questionnaires, thus increasing the response rate. Patient anonymity was maintained by using all obtained patient data to present results at the group level only. Medical charts were accessible only by researchers.

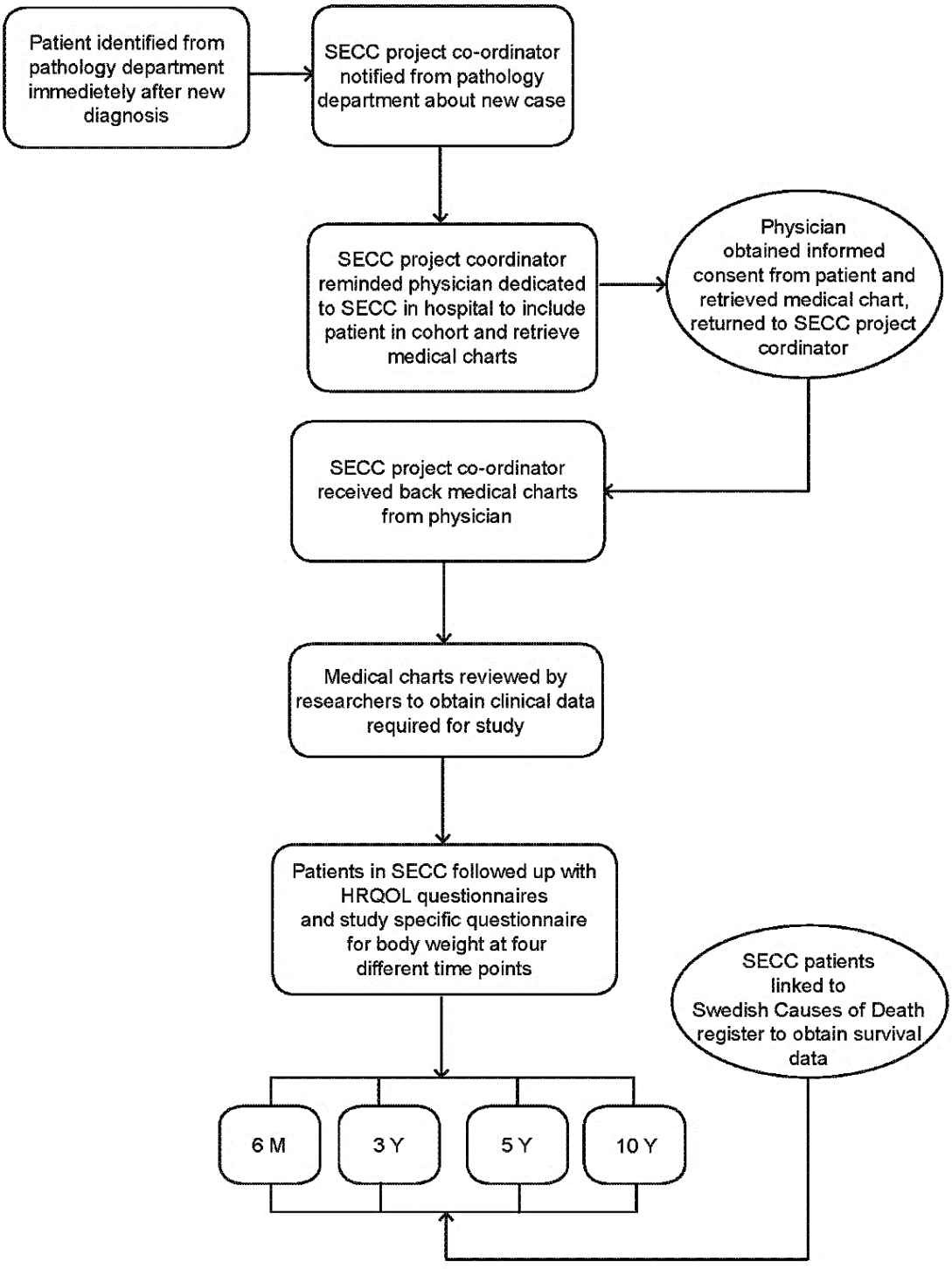

Figure 5. Overview of data collection in SECC cohort.

8.2.2 The Reference Population study

The reference population study is a cross sectional survey conducted on a random sample of adults in the Swedish population (161). The study was conducted with the aim of obtaining HRQOL data in the general population for use as normative reference data for HRQOL assessments in patients with oesophageal cancer. The data collection and sampling were handled by Statistics Sweden, a government organisation that produces official statistics. A sample of 6969 adults in the age group 40-79 years was randomly selected from the general population and invited to participate. Among 4910 (70.5%) participants, 4867 (99.1%) provided complete responses to the HRQOL questionnaires EORTC QLQ-C30 (100) and QLQ-OES18 (102, 116) sent by post to all eligible participants at one single point of time. Each patient in SECC were matched based on age (when HRQOL was assessed), sex, and self-reported co-morbidities (diabetes, cardiac, respiratory, renal or other specified conditions) to the reference population. This resulted in a matching ratio of 1:90 (one patient from SECC to 90 controls from the reference population) (161).

8.2.3 Swedish Causes of Death register

The Swedish Causes of Death register has been in existence since 1952. It encompasses data regarding all deaths among residents in Sweden. Deaths are registered irrespective of whether it occurs in Sweden or outside of the country. The source of data for the underlying cause of death and the date of death are obtained from death certificates issued by physicians according to the latest version of ICD codes. The coverage of deaths in Sweden in the register is more than 99.2% for cause-related deaths occurred since 1952 (162).

8.2.4 Oesophageal Surgery on Cancer Patients Adaption and Recovery (OSCAR)

The OSCAR is a nationwide and prospective cohort study including patients who have undergone curatively-intended surgery for oesophageal cancer in Sweden from 1st January 2013 and onwards. Patients are identified through the pathology departments periodically at the eight hospitals treating oesophageal cancer in Sweden. At one year after surgery the OSCAR project coordinator checked the patients' vital statistics and they were included in the cohort study. Patients are then followed up at regular intervals until five years postoperatively. The OSCAR study has been approved by the Regional Ethical Review Board in Stockholm, Sweden DNR 2013/844-31/1 and all participants provided written informed consent. The overview of the process of data collection in OSCAR is shown in Figure 6.

The data collection was administered by a single project coordinator who handled all inclusions into the study. The information letter followed by a telephone call from the project coordinator, ensured that patients received complete information regarding the project. Patients with cognitive dysfunction and non-Swedish speakers were excluded from participation that were in most cases recognized during the phone call. The date and place of the personal interview was decided by the patient. Patients received professionally printed pre-interview questionnaires by post. All patients provided written consent before the interview for inclusion in OSCAR. The research nurse conducted the interview that included structured interview questions, semi-structured interview questions with open-ended responses, as well as self-report questionnaires completed via touch screen device and the whole visit tape recorded.

The selection of questionnaires included in the questionnaire-battery was the result of several brainstorming meetings and discussions in the research group as well as previous literature. The areas of investigation were thoughtfully selected based on the relevance to oesophageal cancer patients' survivorship. The chosen questionnaire-battery was subjected to a pilot-test among 10 patients before the start of OSCAR data collection. Based on the feedback received from the piloted versions, revisions and improvements were considered. Only minor changes were made to the content of the questionnaire-battery. The questionnaires used in this thesis were the EORTC QLQ-C30 to assess HRQOL, the PG-SGA Short form to assess malnutrition, a study specific questionnaire to assess symptoms of dumping syndrome adapted from Sigstad (163) and Arts questionnaires (164) and a study specific questionnaire to assess dietitian support.

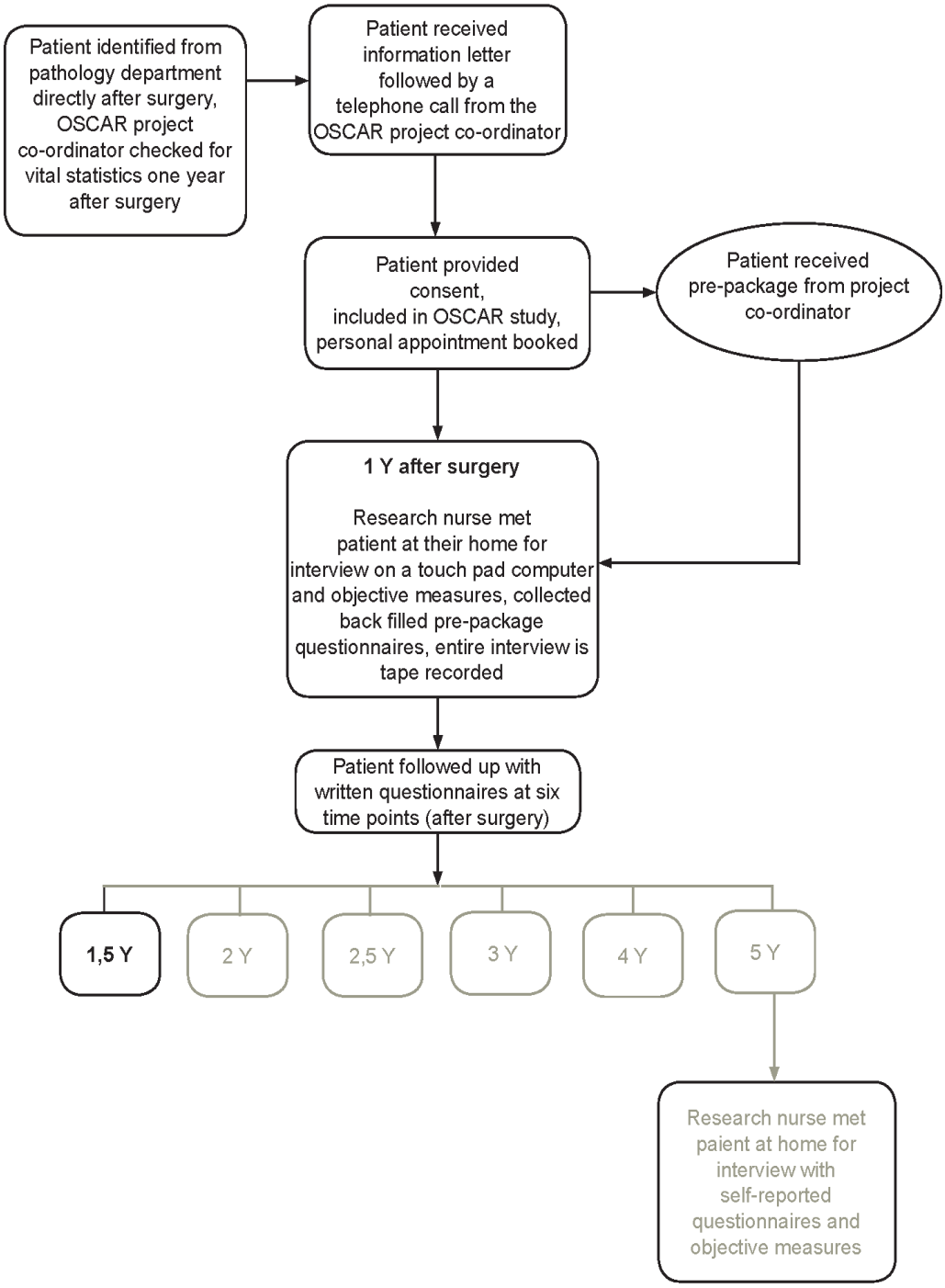

Figure 6. Overview of data collection process in OSCAR cohort.

Patients were followed up at six fixed time points after the interview ending five years after the surgery. Before each follow-up questionnaire was sent to the patient, a personal phone call by the project coordinator was made to each patient. In this thesis, data collected in OSCAR at the one-year interview and one and half year follow-up was used.

Clinical data at the time of operation was obtained from medical records. Medical records are requested from the respective hospitals where the patients were operated. The medical records are thoroughly scrutinised by a group of researchers and clinicians according to a pre-defined study protocol to ensure consistency and uniformity of the data collection. The clinical data collected includes 1) tumour histology, site and stage (histopathology reports), 2) treatment (operation reports) and, 3) length of stay in hospital. In **Studies III and IV** of this thesis, 217 patients included in OSCAR who were operated between 1st January 2013 and 31st December 2016 and for whom clinical data were collected were included.

The comprehensive, nationwide and prospective data collection improved the validity. The personal contact with the patients before inclusion and before every follow-up and the personal interview-based approach improved the response rate and reduced frequency of missing items. Moreover, the accuracy from the written questionnaires to the data entered in the system was validated in a random sample of 20 patients and was found to contain low frequency of errors for the one year and (error margin = 0.65%) and one and half year (data collected in OSCAR (error margin = 0.33%).

8.3 STUDY DESIGN

All Studies I –IV are nationwide, population-based prospective cohort studies of patients who underwent curative surgery for oesophageal cancer in Sweden.

Studies I and II were based on SECC cohort that included patients who were operated from 2nd April 2001 to 31st December 2005 (Figure 5). **Study I** included outcome data on HRQOL and weight assessments from follow-ups at six months, three, five and 10 years. **Study II** included data from the six-month follow-up**.**

Studies III and IV were based on patients included in the OSCAR cohort who underwent surgery during the period from 1st January 2013 to 31st December 2016 (Figure 6). **Study III** included follow-up data at one and half years after surgery. **Study IV** included data from the interview at one year after surgery.

8.3.1 Study exposures

Study I: The study exposure was presence of eating difficulties and weight loss over the course of six months, three, five and 10 years after surgery for oesophageal cancer. **Eating difficulties**: Yes/No from the eating difficulty scale (EORTC QLQ-OES18, questions 36-39) (116). 'Yes' was defined as 'quite a bit' or 'very much' on any item. 'No' was defined as 'not at all' or 'little' on all items. **Weight loss:** $< / \geq$ median percentage weight loss of the study population. Percentage weight loss was calculated as [(weight (kg) at current follow-up time

point – weight (kg) at previous follow-up time point)/ (average weight (kg) as an adult)] × 100. To assess the combined effect of eating difficulties and weight loss four exposure groups were defined,

Table 2. Overview of exposure groups in **Study I**.

		Percentage weight loss	
		<median	≥median
Eating difficulties	No	Group 1 (reference)	Group 2
	Yes	Group 3	Group 4

Study II:

The study exposure was nutritional problems defined as the presence of nutrition impact symptoms and weight loss experienced at 6 months after surgery for oesophageal cancer. **NIS**: Symptoms assessed using EORTC QLQ-C30 (100) and OES18 (116) were mapped to the common NIS (149) in patients with cancer and categorised as '0-1 symptoms' and 'at least 2 symptoms'. **Weight loss:** < / ≥ median percentage weight loss calculated as [(weight (kg) at six months after surgery – weight (kg) at surgery)/ (average weight (kg) as an adult)] × 100. To assess the combined effect of NIS and weight loss four exposure groups of nutritional problems were defined,

Table 3. Overview of exposure groups in **Study II**.

		Percentage weight loss	
		<median	≥median
NIS	No	Low (reference)	Moderate
	Yes	Severe	Very severe

Study III:

The study exposure was symptoms of early and late dumping syndrome assessed using a study specific questionnaire. The symptoms were further categorised as 1) severe (at least 2 symptoms with a severity of 'quite a bit' or 'very much'; 2) moderate (at least one symptom with a severity 'not at all', 'a little', 'quite a bit' or 'very much') and 3) none (no dumping symptoms - reference group).

Study IV:

There were two study exposures 1) initiation of dietitian support categorised as preoperative or postoperative 2) patient reported satisfaction with dietitian support categorised as high or low. Both exposures were assessed using a study specific questionnaire. The satisfaction of dietitian support was reported by patients on a scale of 1-7 where 1 = not at all good and 7 = extremely good, and a score of 1-5 were defined as low and 6-7 as high.

8.3.2 Study outcomes

All HRQOL outcomes in **Studies I-III** were assessed using EORTC QLQ-30 version 3.0.

Study I

The study outcome was changes in HRQOL from before surgery to six months, three, five and 10 years from surgery. The reference population study was used as proxy HRQOL scores before diagnosis.

Study II

The study outcomes were six months postoperative HRQOL and overall five-year survival. The selected aspects of HRQOL were global QOL, social and physical function.

Study III:

The study outcome was postoperative HRQOL at one and half year after surgery for oesophageal cancer. The primary HRQOL outcome was summary score and secondary outcomes were global QOL, functional aspects of HRQOL (physical, role, emotional, cognitive and social).

Study IV:

The study outcome was nutritional status that had two components 1) percentage postoperative weight loss and 2) NIS score. Percentage postoperative weight loss was calculated as [(weight (kg) before surgery – weight (kg) at one year after surgery)/ (average weight (kg) as an adult)] × 100. NIS score was ascertained from PG-SGA Short form as an additive score of each symptom (0=low impact on nutritional status; 1=mild; 2=potentially severe). A score ≥ nine reflects a need for nutritional intervention or clinical management (150).

8.4 STATISTICAL ANALYSIS

Mean scores for each HRQOL outcome was obtained by transforming the responses from the EORTC QLQ-C30 to a linear scale score of 0-100 (raw mean scores) as per the EORTC scoring manual (165). A complete case analysis were conducted to handle missing values owing to very few missing cases according to the EORTC guidelines (165). All statistical analyses were conducted using SAS® version 9.4 (SAS Institute, Cary, North Carolina, USA).

Study I:

Differences in mean scores were calculated as change between two follow-up time points i.e. a) six months – baseline; b) three years – six months; c) five years – three years; d) 10 years – five years. A longitudinal statistical model of repeated measures ANOVA was used to calculate the adjusted change in HRQOL for the combined effect of eating difficulties and weight loss. The model adjusted for age (continuous), sex (male/female), BMI (<25/≥25), tumour stage (0-I/II/III/IV), co-morbidities (no/yes) and time. The interpretation of the differences in HRQOL based on what is a clinically important difference for patients were assessed with the evidence-based guidelines. The longitudinal guidelines were used to interpret the clinical relevance of HRQOL scores between the time points (166) and the evidence based cross-sectional guidelines were used for the differences between the exposure groups (167). Additionally, for clinically relevant differences between the exposure groups, a t-test was performed for testing the statistical significance at a level of $p < 0.050$.

Study II:

Adjusted mean difference (MD) for the HRQOL outcomes were calculated from ANCOVA regression models by deducting the adjusted mean score of the reference exposure group from the adjusted mean score of the respective exposure group. The evidence based cross-sectional guidelines were used to interpret the differences between the exposure groups (167). The overall five-year survival among the exposure groups were assessed using a Cox proportional hazards model presented as hazard ratio (HR) with 95% CI. Both the ANCOVA and survival models were adjusted for age (continuous), sex (males/females), co-morbidities (0/1/>2), histology (adenocarcinoma and dysplasia/squamous cell carcinoma), tumour stage (0-I/II/III/IV), tumour location (upper and middle/lower and cardia), operation type (oesophageal resection/cardia resection/extended total gastrectomy/total gastrectomy and oesophageal resection), postoperative complications (no/yes). To account for the effect of preoperative BMI all analyses were stratified for low BMI (<25) and high BMI (≥ 25).

Study III:

Adjusted MD for the summary score, global QOL and functional scales were calculated from ANCOVA regression model as (adjusted mean score of the reference exposure group-adjusted mean score of the respective exposure group). The model was adjusted for age (continuous), sex (male/female), co-morbidities (0/1/>2), neoadjuvant therapy (yes/no), tumour stage (0-I/II/III-IV/other), tumour histology (adenocarcinoma and dysplasia/squamous cell carcinoma/neuro endocrine carcinoma), surgical approach (minimally invasive/hybrid thoracotomy/laparoscopic/open oesophagectomy), postoperative complications (low grade (CDS 0-II/CDS III-IV), postoperative eating difficulties (No/Yes). The evidence based cross-sectional guidelines were used to interpret the differences between the exposure groups (167).

Study IV:

An ANCOVA regression model was performed to obtain adjusted MD as differences in means between the percentage postoperative weight loss and NIS score in the comparison groups of pre and postoperative dietitian support and low and high satisfaction of the dietitian support. The model was adjusted for age (continuous), sex (male/female), co-morbidities (0/1/>2), preoperative BMI (continuous), neoadjuvant therapy (yes/no), tumour stage (0-I/II/III-IV/other), tumour histology (adenocarcinoma and dysplasia/squamous cell carcinoma/neuro endocrine carcinoma), surgical approach (minimally invasive/hybrid thoracotomy/laparoscopic/open oesophagectomy), postoperative complications (low grade (CDS 0-II/CDS III-IV), pre and postoperative enteral/ parenteral nutrition support (intensive/medium/normal) and recurrence (yes/no). A sensitivity analysis was conducted on the satisfaction with the dietitian support scale (1-7) by removing the score of 5 from the scale to test its uncertainty in the model.

9 RESULTS

A selection of patient characteristics included in **Studies I-IV** in this thesis are shown in Table 4.

Table 4. Overview of patient and tumour characteristics according to **Studies I-IV**.

	Study			
	I	**II**	**III**	**IV**
Number of patients	92	358	144	180
Sex, number (%)				
Male	73 (79)	291 (81)	120 (83)	148 (82)
Female	19 (21)	67 (19)	24 (17)	32 (18)
Mean age, years (range)	63 (31-79)	66 (31-85)	66 (30-84)	66 (30-84)
Co-morbidity, number (%)				
0	44 (48)	203 (57)	77 (54)	94 (52)
1	29 (32)	90 (25)	42 (29)	54 (30)
>2	19 (21)	65 (18)	25 (17)	32 (18)
Preoperative BMI, number (%)				
<=25	42 (46)	162 (47)	43 (36)	52 (35)
>25	49 (54)	196 (55)	78 (64)	96 (65)
Tumour stage, number (%)				
0-I	49 (53)	80 (23)	36 (25)	38 (21)
II	29 (32)	112 (32)	55 (38)	67 (37)
III-IV	14 (15)	162 (45)	36 (25)	55 (31)
Unknown	0 (0)	0 (0)	17 (12)	20 (11)
Tumour histology, number (%)				
Squamous cell carcinoma	20 (22)	82 (23)	23 (16)	30 (16)
Adenocarcinoma and dysplasia	72 (78)	276 (77)	120 (83)	149 (83)
Neuro endocrine carcinoma	0 (0)	0 (0)	1 (1)	1 (1)

9.1 STUDY I

In total, of 616 patients who underwent oesophagectomy during the study period, 92 who were alive at 10 years and responded to all four HRQOL questionnaires were included in the study. Regarding weight changes, the greatest weight loss (12%) was observed at six months from surgery and was higher among those with eating difficulties compared to no difficulties with eating (15% vs 9%).

Concerning changes in HRQOL over time, global QOL deteriorated across the trajectory in those with eating difficulties and >median weight loss (Figure 7). For those with eating difficulties and <median weight loss, the worsening was significant at three of the four follow-up points. These changes were clinically and statistically significant.

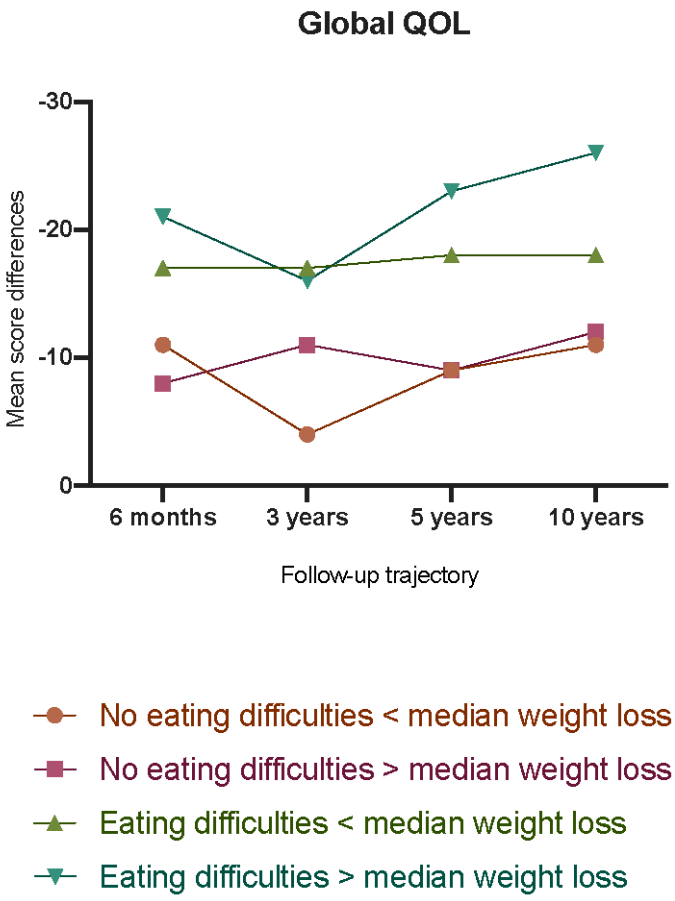

Figure 7. Changes in Global QOL over time in patients as per the four groups of eating difficulties and weight loss.

Among functional scales the number of aspects that deteriorated over time was highest among those with eating difficulties and >median weight loss at six months (four out of five aspects) and 10 years (five out of five aspects, Figure 8a). Among symptom scales and items, those with eating difficulties and weight loss, experienced significantly worsening symptoms in the most number of aspects across the trajectory (Figure 8b). The changes in social function and diarrhoea across the follow-up trajectory are shown in Figure 9a and 9b respectively. All changes were clinically and statistically relevant.

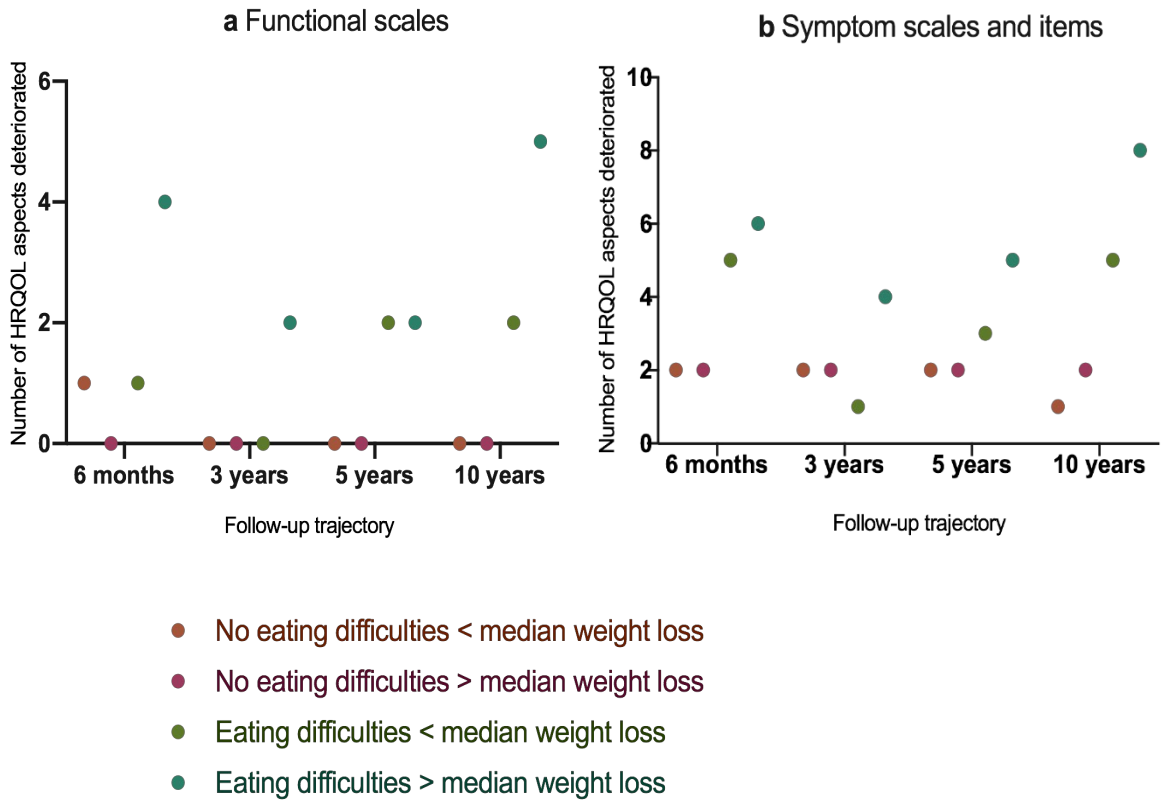

Figure 8. Number of **a.** functional aspects, **b.** symptom scales and items, that were worse in patients with four different levels of eating difficulties and weight loss across a trajectory of follow-up from surgery to 10 years postoperatively.

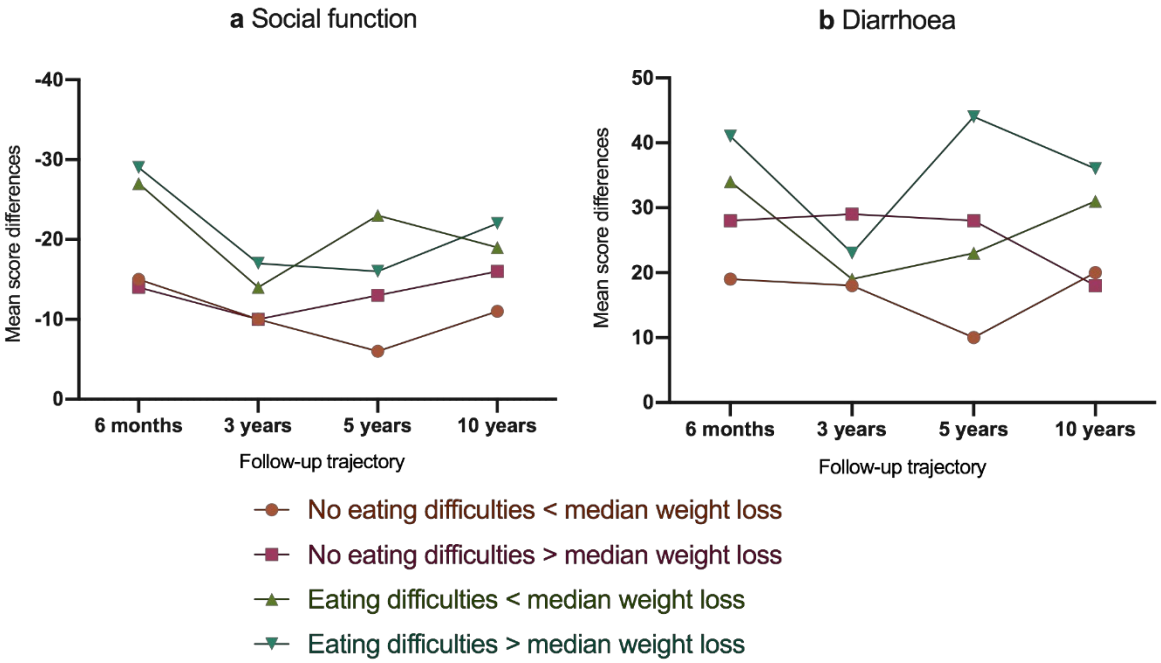

Figure 9. Changes in **a.** social function, **b.** diarrhoea, over time in patients as per the four exposure groups of eating difficulties and weight loss.

Figure 10 illustrates the number of follow-up time points at which the HRQOL outcomes worsened among the three exposure groups compared to the reference group (between group differences). Those with eating difficulties and >median weight loss worsened in all 15 aspects of HRQOL outcomes in at least one-time point. Among the HRQOL outcomes, appetite loss was worse at all the four follow-up points and diarrhoea at three out of four-time points. Those with eating difficulties and <median weight loss had worse HRQOL outcomes in six aspects out of 15 compared to the reference group. For those with no eating difficulties and >median weight loss only one aspect out of 15 was worse compared to the reference group. All changes were clinically and statistically relevant.

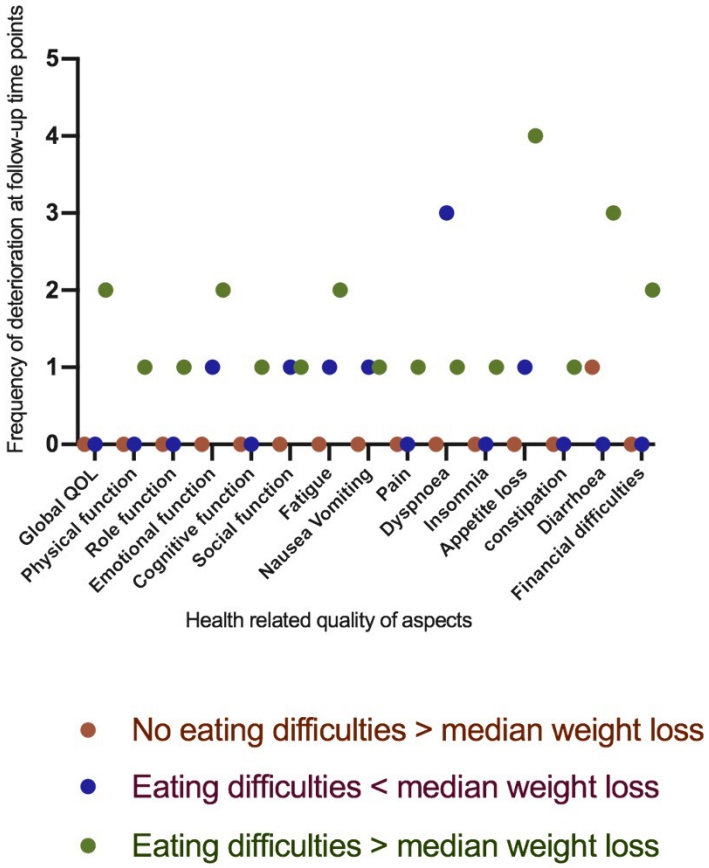

Figure 10. Number of follow-up time points at which HRQOL aspects were worse for the three exposure groups compared to reference exposure group.

9.2 STUDY II

Among 616 patients who underwent operation for oesophageal cancer, 358 (79%) patients answered both questionnaires related to exposure and outcomes and were included in the study. Of those included 162 (47%) had a low BMI (<25) preoperatively and 196 (55%) had a high BMI (≥25). The distribution of the four exposure groups among those with low and high preoperative BMI are shown in Figure 11a and b. Very severe nutritional problems were experienced by the largest proportion in both BMI groups.

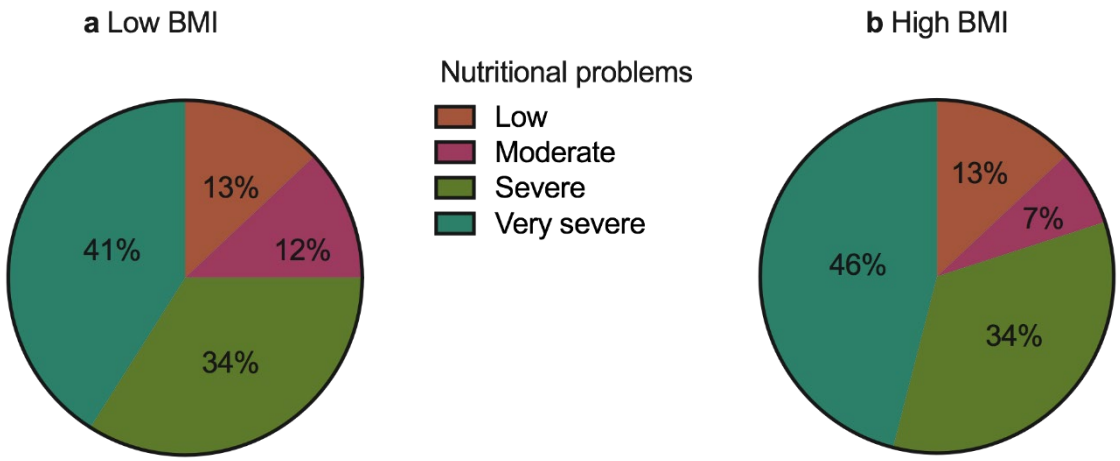

Figure 11. Distribution of the four exposure groups of nutritional problems stratified by **a.** Low preoperative BMI <25, **b.** High BMI preoperative BMI ≥25, Nutritional problems: Low - ≤1NIS <median weight loss; Moderate - ≤1NIS >median weight loss; Severe - ≥2NIS <median weight loss; Very severe - ≥2NIS >median weight loss.

HRQOL, the mean scores of global QOL, social and physical function for the four groups of nutritional problems are illustrated in Figure 12. For those with moderate nutritional problems, the differences in mean scores compared to low nutritional problems were not significant clinically and statistically in both low and high BMI categories. However, for both groups with severe and very severe nutritional problems, the differences in means scores for global QOL, social and physical function were both clinically and statistically relevant compared to those with low nutritional problems in both BMI groups. The HRQOL outcomes between the two groups of BMI did not differ significantly with clinical relevance.

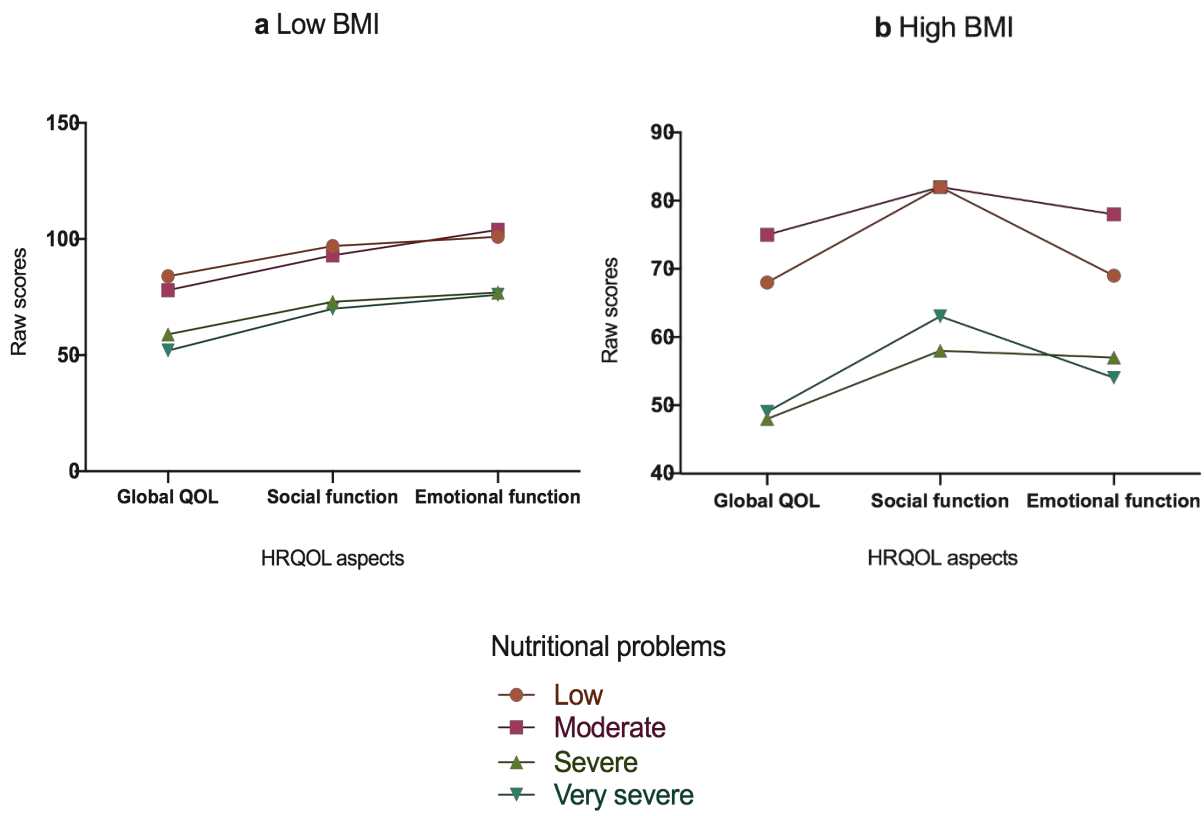

Figure 12. HRQOL outcomes among the four exposure groups based on severity of nutritional problems stratified by **a.** Low preoperative BMI <25, **b.** High BMI preoperative BMI ≥25, Nutritional problems: Low - ≤1NIS <median weight loss; Moderate - ≤1NIS >median weight loss; Severe - ≥2NIS <median weight loss; Very severe - ≥2NIS >median weight loss.

The survival analysis showed a worse survival among those with high preoperative BMI with very severe nutritional problems compared to low nutritional problems with high BMI before surgery (HR 4.64, 95% CI: 1.38 to 15.56). No statistically significant differences in survival were observed in those with moderate and severe nutritional problems in either BMI categories.

9.3 STUDY III

Among 309 patients who were operated for oesophageal cancer and eligible for inclusion in the study, 144 (73%) answered both questionnaires regarding exposure and outcome and had sufficient clinical data for the final analyses. The prevalence of moderate and severe symptoms of early and late dumping syndrome in the study population is shown in Figure 13. Early dumping symptoms with moderate severity was the most prevalent group.

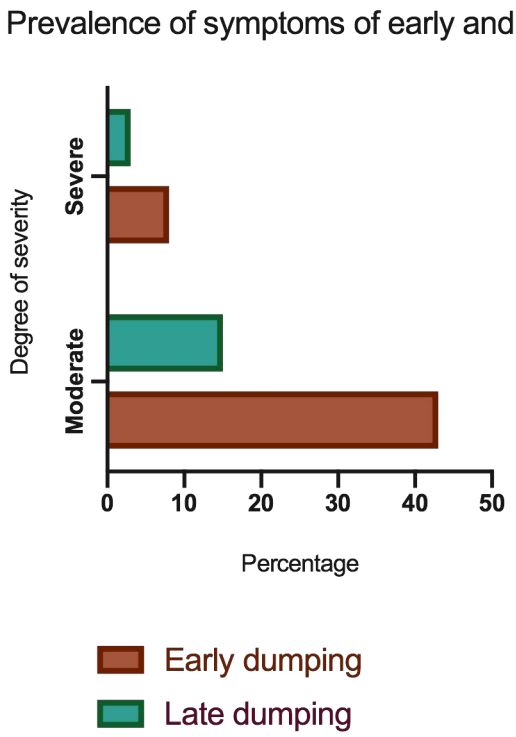

Figure 13. Distribution of symptoms of early and late dumping syndrome with moderate and severe symptom severity experienced at one year after surgery for oesophageal cancer.

The raw scores of HRQOL outcomes between those with no dumping, moderate early dumping and severe early dumping are illustrated in Figure 14a. Emotional function was worse (MD -11, 95% CI: -18 to -4) in those with moderate early dumping compared to no dumping with clinical (medium) and statistical significance. Comparatively, severe early dumping was associated with poorer global QOL (MD -18, 95% CI: -32 to -3) compared with no dumping, that was clinically large and statistically significant.

The raw scores of HRQOL outcomes between those with no dumping, moderate late dumping and severe late dumping are illustrated in Figure 14b. The mean summary score (MD -17, 95% CI: -26 to -8) and global QOL (MD -14, 95% CI: -25 to -2) in those who had moderate late dumping were lower with clinically medium relevance and further of statistically significance compared to no dumping. Moderate late dumping was also associated with clinically medium and statistically significant poorer role, cognitive and emotional functions and worse social function (MD -23, 95% CI: -38 to -8) to a clinically large relevance. Severe late dumping was related to a lower mean summary score (MD -21, 95% CI: -39 to -2), cognitive function (MD -30, 95% CI: -53 to -7) and emotional function (MD -39, 95% CI: -63 to -15) compared to the no dumping group. The MD were clinically large and statistically significant.

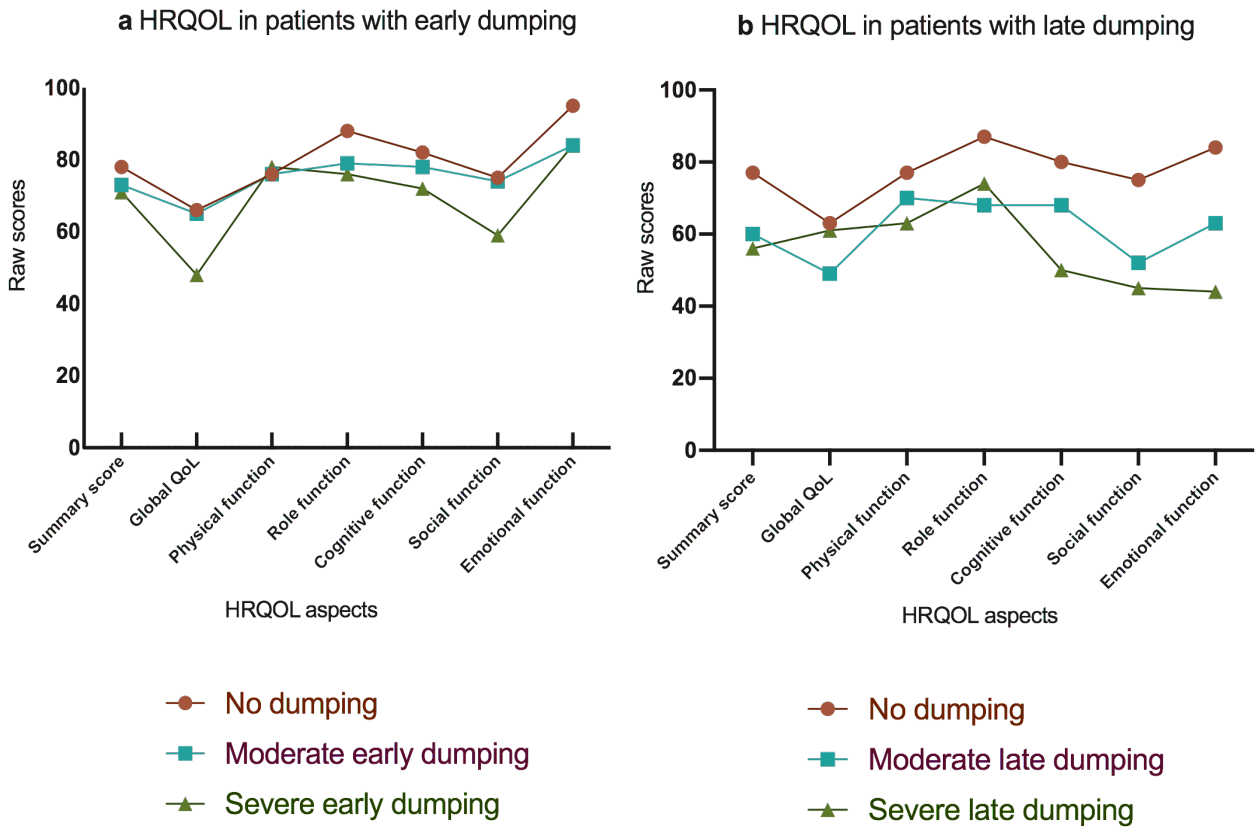

Figure 14. HRQOL in patients with **a.** symptoms of moderate and severe early dumping, **b.** symptoms of moderate and severe late dumping compared patients with no dumping (reference group).

9.4 STUDY IV

In total 309 (100%) patients who were alive at one year after operation and reachable were eligible for inclusion. Among them, a total of 180 (83%) patients answered both questionnaires regarding the exposures and outcomes and had clinical data required for this study and were included in the final analyses. The mean preoperative percentage weight loss among those who received preoperative dietitian support was 4% and among those who receive only postoperative support was none (0.4%). The mean and median weight loss at one year after surgery were both 11% respectively and the mean NIS score was 2.

Postoperative nutritional status according to when dietitian support was initiated is illustrated in Figure 15a. As much as 55% of patients had dietitian contact preoperatively with a mean postoperative weight loss of 10%. The mean postoperative weight loss among those who received postoperative dietitian support only was 12%. The NIS scores among the pre and postoperative dietitian contact groups were 2 and 3 respectively. There were no statistically significant MD in percentage postoperative weight loss (MD 1, 95% CI: -2 to 4) and NIS

scores (MD 1, 95% CI: 0 to 2) between those who received preoperative and postoperative dietitian support compared to only postoperative dietitian support.

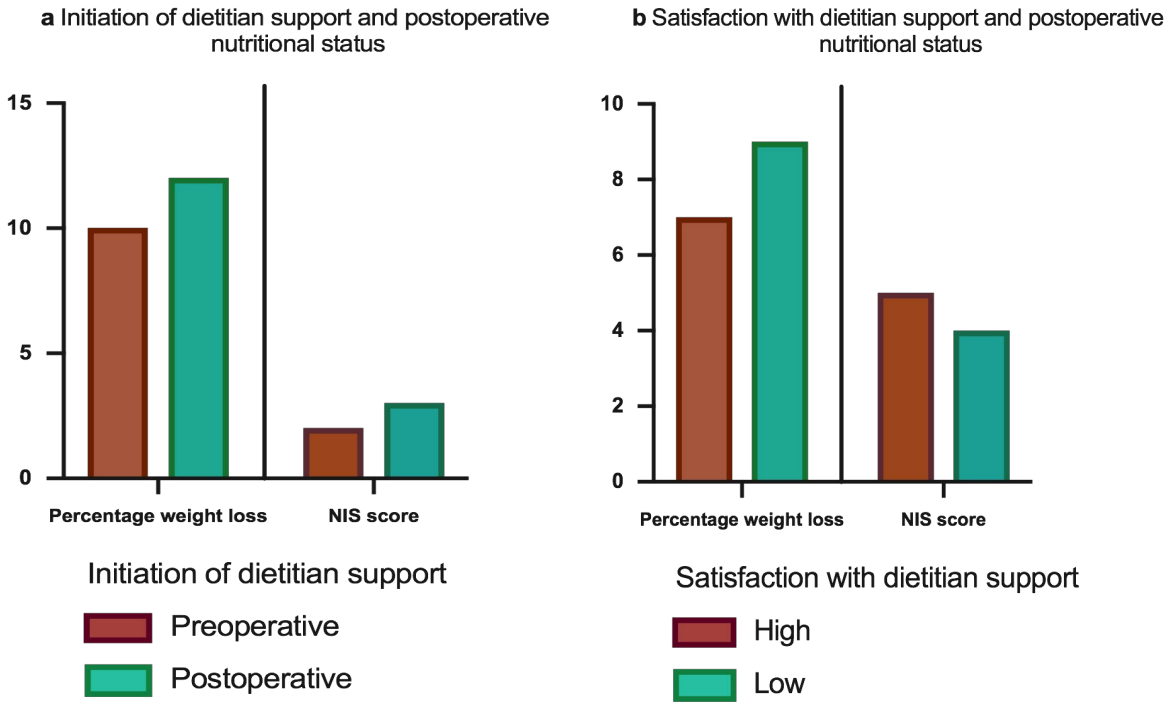

Figure 15. Nutritional status at one year after surgery for oesophageal cancer according to **a.** Initiation of dietitian support, **b.** Satisfaction with dietitian support.

A high satisfaction with the dietitian support they received were reported by 71% of patients that increased to 84% after removing the number five from the scale in the sensitivity analysis. Nutritional status according to patient reported satisfaction with the dietitian contact is graphically presented in Figure 15b. Those who reported high satisfaction had a mean postoperative weight loss of 7%. Among those who reported low satisfaction of the support, the weight loss was 9%. The difference in percentage postoperative weight loss between patients who reported high and low satisfaction was statistically non-significant (MD 1, 95% CI: -2 to 5). After the sensitivity analysis, the weight loss for the pre and postoperative dietitian support was 14% and 11% with still a statistically non-significant mean difference. The mean NIS score for patients who reported high satisfaction was 5 and for those who reported low satisfaction was 4. The mean differences were statistically non-significant (MD -1, 95% CI: -2 to 1). Following the sensitivity analysis, the mean NIS scores were 3 for both the groups reporting high satisfaction and low satisfaction and hence still non-significant between the groups.

10 DISCUSSIONS

10.1 METHODOLOGICAL CONSIDERATIONS

In the science of clinical epidemiology, predictions are made about individual patients by counting the most important health outcomes (5D's – disease, discomfort, dissatisfaction, disability, death) in groups of similar patients (108). Strong scientific methods are required to ensure that the predictions are accurate.

10.1.1 Study design

In order to address research questions in clinical epidemiology, design of studies can be either observational or experimental (intervention studies). In an observational study, the course of a disease or the association between risk factors (exposures) and outcomes is observed by the researcher. In an experimental study, an intervention is done by the researcher to prevent the onset of disease or change its course in study populations. It is ideal in an epidemiological study if all factors, except the one under study, are identical between the study participants in the comparison groups e.g. treatment arms in an experimental study or exposed unexposed in an cohort study (108). In this context, experimental studies are considered superior in the hierarchy of study designs as individuals are randomly allocated to the intervention or control group and the randomisation accounts for the distribution of dissimilarities between both groups equally (168). However, not all designs can be experimental since it may be unethical or impractical to conduct interventions in some cases. **Studies I-III** in this thesis could not be experimental in design for the same reason that it would be unethical and unfeasible to assign weight loss, eating difficulties or NIS to patients in **Studies I and II** or symptoms of dumping syndrome in **Study III.** Although it would have been feasible to randomise patients to pre and postoperative dietitian support in **Study IV** this would also be unethical. In such a scenario, an observational study is designed with an attempt to mimic the effects of an experimental design. Observational studies include cross sectional, cohort, case-control, and ecological studies. **Studies I-IV** in this thesis are all cohort studies. A cohort is a group of individuals who underwent a similar experience or shared the same condition, in this thesis having undergone oesophageal cancer surgery. In a cohort study, patients are grouped based on their exposure status as exposed and unexposed and followed up for the occurrence of the outcome. For e.g., in **Study III** in this thesis, patients with symptoms of dumping (exposed) and no dumping (unexposed) were followed up regarding HRQOL

(outcome). Although not ranked as high as experimental studies, cohort studies can provide strong evidence if designed appropriately (168). Some argue that cohort studies are by definition prospective in nature. However, cohort studies can be prospective, or retrospective based on when outcomes occurred in relation to the enrollment of the cohort. In a prospective cohort study the subjects are enrolled and baseline data collected before any subjects develop the outcome of interest. In retrospective cohort studies, the exposure and outcomes have already occurred at the time of data collection. They are usually conducted on data that already exists (from prospective studies) and the exposures are defined before looking at the existing outcome data to see whether exposure to a risk factor is associated with the outcome. All **Studies I- IV** in this thesis were prospective cohort studies. A cohort study design has the advantage of minimizing selection bias and information bias (recall bias) by taking temporality into consideration, i.e., exposure occurs before the outcome. The limitations may however be that they are more expensive and may have a higher risk of loss to follow-up.

10.1.2 Validity

The quality of a study in clinical research is assessed as a measure that is equivalent to its validity. Last defined validity as the "degree to which the inference drawn from a study is warranted when account is taken of the study methods, the representativeness of the study sample, and the nature of the population from which it is drawn" (169, 170). In 1950, Campbell further introduced the distinction between internal and external validity into the concept of validity (170). Internal validity is the extent to which a study data actually measures what they were intended to measure. External validity is the extent to which the results of the study can hold true in other settings. There are three key factors that affect validity - bias, confounding, and precision.

10.1.2.1 Bias

A bias is a systematic error introduced at any stage of inference that can distort the estimation of an epidemiological measure. The presence of bias in epidemiological studies by itself does not necessarily render them as unacceptable. It is necessary to assess the probable impact that the various biases may impose on the results in terms of the direction and the magnitude. The magnitude should not be large enough to make the results stronger or weaker than those observed. There are two main types of bias that are of major concern – selection bias and information bias.

10.1.2.1.1 Selection bias

Selection bias arises when comparisons are made between groups of patients that differ in ways other than the main factors under study i.e., systematic differences between comparison groups, that in turn affects the outcomes of the study. In a cohort study, selection bias arises mainly from non-participation i.e., differences in characteristics between those who take part in a study and those who do not, if these differences are themselves related to the outcome. Then the comparison between the groups are biased and little can be concluded about the independent effect of the characteristic of interest (108).

Studies I-II in this thesis included essentially all patients who underwent surgery for oesophageal cancer from the entire Swedish population across the country. The project coordinator was informed by the pathology departments about all operated patients and could ensure that no patient was excluded or not reported by the treated hospital. Since there may be a risk of not reporting poor cases from the treating hospitals. The non-participation was only due to non-participating hospitals and not owing to patient's unwillingness to participate or owing to a selection of only good cases by the treating hospitals. Moreover, when one hospital did not participate both good and/or bad cases were lost, and this may be considered better than losing patients from various hospitals. The population-based design with a high participation rate of 90% minimized the risk of selection bias in **Studies I and II**.

Selection bias may also arise from loss to follow-up i.e., non-responders at the follow-up of **Studies I-II.** However, when tested for statistically significant differences in sociodemographic and clinical characteristics between the responders and non-responders at each follow-up point, no differences were found in **Studies I and II** indicating a low risk for selection bias. **Studies III-IV** in this thesis included data collected on a nationwide population of patients who underwent surgery for oesophageal cancer in Sweden. The collection of exposure and outcome data was carried out by a research nurse in the patients' homes, thus missing data was minimal. On the other hand, selection bias could still have been introduced from those who were not reachable and those who denied participation. For e.g., 12% of patients who were not reachable, died within one and half years from surgery. Moreover, the non-response of 26% at one and half years after surgery in **Study III** regarding the outcome may have introduced a selection bias. Also, the clinical data

being obtained by clinicians not directly involved in the care of the patients reduced selection bias as this is objective and not selective data collection in **Studies I to IV**.

10.1.2.1.2 Information bias

Information bias occurs when there are systematic errors in measurement causing misclassification of the study variable. The source of the error in measurement may arise from the selection of tools to obtain the study measures or may arise from the assessor's attitude and the cooperation of the participant, in a human based study. The misclassification is categorised as differential when it is different between the comparison groups and non-differential when it is not different between the comparison groups. Non-differential misclassification tends to dilute risk associations toward the null and is mainly a problem in studies showing no associations. While, a differential misclassification can lead to biased risk estimates in both directions.

Studies I-IV includes a prospective, well-structured data collection and medical charts were scrutinized using a pre-defined study protocol for data extraction. The study coordinator made sure that the data collection was complete and correct which should reduce misclassification. Furthermore, data gathering for clinical variables for **Studies I to IV** was conducted by personnel not directly involved in the study and unaware of the exposure status of each participant, further reducing the risk of information bias. The outcome measure for the survival data was obtained from linkage of the cohort to the highly valid Swedish causes of death register by means of the patient's unique personal identity number reduced misclassification for survival outcomes in **Study II**.

When dealing with PROMs as the main outcome, both differential and non-differential misclassification may occur. Differential misclassification may occur since the patients' responses to questionnaires may be influenced by the interviewer. To avoid this bias, all assessments were made by means of mailed questionnaires in **Studies I and II**. Due to the subjective nature of HRQOL measurements, non-differential misclassification may occur as questionnaires may fail to precisely allocate patients into subgroups. The use of validated instruments and the use of previously used cutoff should minimize this risk. Part of the exposure in **Studies I and II**, eating difficulties and NIS were obtained from validated questionnaires. Similarly, all HRQOL outcomes were also obtained using well validated questionnaires reducing the scope for misclassification. In **Studies III and IV** misclassification of the exposure could be influenced by the use of a non-validated

questionnaire for measurement of dumping symptoms and dietitian support. However, the OSCAR dumping questionnaire was adapted from two commonly used dumping questionnaires, the Sigstad' s score (163) and the Arts dumping questionnaire (164). The OSCAR dumping questionnaire was also piloted in a group of test patients and the face validity of the questions was considered good.

In **Studies I and II** in this thesis, the weight loss component of the exposure was derived from self-reported weight by the patients and not measured objectively and hence may be a source of information bias. However, the analysis of self-reported preoperative bodyweight compared with that measured by surgical staff before operation showed good validity (correlation coefficient 0.77) in this patient group (8). Hence the risk of misclassification should be small with regards to subjectively reported weight since weight loss is a central issue for patients with oesophageal and hence are likely to recall their weight more accurately. Likewise, in **Study IV**, since weight loss and NIS are central problems for patients with oesophageal cancer, recall of meeting the dietitian should not have been recalled incorrectly.

10.1.2.2 Confounding

Confounding happens when the exposure is influenced by a third factor, which is itself related to the outcome, owing to which the effect of the exposure can be confused with the third variable. Confounding is however not the intermediate step in the exposure outcome association, but it spuriously influences the risk estimates. In the event that the effect of the confounder is not accounted for, it distorts the observed association. In all **Studies I-IV**, the availability of patient and clinical data from the medical charts allowed for adjustment for potential confounders that may affect the outcomes of the studies. Confounding can be controlled for in many possible ways. In this thesis, stratification was used to control for BMI in **Study II** and a multivariable regression analysis was used across all studies to account for However, residual confounding may still be present due to unmeasured confounding e.g. lifestyle factors such as tobacco smoking and alcohol and cannot be fully disregarded.

10.1.2.3 Precision

Precision is defined as consistency in results when a measurement is repeated. Precision is inversely proportional to the amount of random error that is present in a study i.e., the higher the random error the lower the precision. Random error minimizes with increase in

the sample size of a study that is reflected in the confidence intervals (CI) and p-value. The most common CI set at 95% indicates that when the study is repeated any number of times, it would yield a point estimate within the obtained CI 95% of the time. The corresponding p value of < 0.05 is the significance (alpha) level which represents the probability that random fluctuations alone could have generated results that differed from the null hypothesis in the direction of the alternative hypothesis (171). The null hypothesis assumes that any effect seen in the data is merely the result of random fluctuations and does not reflect any real association between the exposure and the outcome. The alterative hypothesis assumes the presence of real association between the exposure and outcome and the association is above that attributed to random fluctuations (171). With a $p < 0.05$ the null hypothesis is rejected, and the alternative hypothesis is accepted. A $p < 0.05$ is an arbitrary value that is more commonly used but can be lowered to 0.01 or 0.0001 for more precision. The alpha is in fact the probability of making a type I error i.e., getting a significant result, when in fact no effect is present. To reduce the possibility of a type I error, the exposures and outcome were pre-defined in a study protocol, only clinically relevant factors in the multivariable analysis were used, for all **Studies I-IV** in this thesis. Moreover, the number of hypothesis were restricted in **Studies II and III** by selecting only a few HRQOL aspects as the outcome. On the other hand, a beta is the probability of making a type II error i.e., failing to get a significant result when in fact some effect is actually present. A type II error is minimized with a larger sample size, exposure and outcome of good quality and a well-designed study. The overall sample size of **Studies I, II and IV** in this thesis were sufficient because of perceived moderate effect size between comparison groups and hence should have lowered the risk of a type II error. The overall low sample size in **Study III**, stratified sample size in **Study II** and within each exposure group in all **Studies I-IV** may have increased the risk for type II error. But since there was no borderline significance observed in the p values, it can be considered that the risk of type II errors was low.

10.1.2.4 Generalisability

External validity or generalisability is the extent to which the results of a study can be applied to the larger populations from which the sample was drawn and to similar populations and settings than the one where it was conducted. All **Studies I-IV** are population-based studies in Sweden hence providing good generalizability to Scandinavian populations with similar demographics, diagnostics, treatment and tumour histology. The data used in **Studies I and II** were collected during 2001–2005 and may affect the

generalisability owing to changing clinical treatment regime. However, the results of **Studies I and II** in this thesis are independent of the type of treatment and thus may not be a big issue in the clinical interpretation of the results. Moreover, the ten-year follow-up for SECC ended in December 2015 which is much more recent and hence the generalisability regarding the exposure and HRQOL outcomes are from much more recent data in **Study I**.

10.1.3 Causality

Considering the multifaceted nature of HRQOL and the myriad of factors which can influence it, it is extremely hard to demonstrate causal association in PROMs research. Moreover, many criteria usually used for judgment of causal associations cannot be used in this setting (e.g. biological gradient, biological plausibility, experimental evidence). The overall aim of the studies included in this thesis were to find whether there are nutritional factors which may influence the HRQOL of patients after oesophageal cancer surgery in order to identify potential targets for interventions, rather than looking for causal inference.

10.1.4 Interpretation of HRQOL scores

The EORTC QLQ-C30 were used in **Studies I-III** owing to its well-recognized psychometric properties and QLQ-OES18 was used in **Studies I and II** to capture oesophageal cancer specific symptoms. The responses for all scales and single items on the QLQ-C30 and QLQ-OES18 are assessed on a four-point Likert scale: 1 - Not at all; 2 - A little; 3 - Quite A Bit; 4 - Very much, except for the global QOL scale on the QLQ-C30 which is measured on a scale ranging from 1-7, where 1 being the lowest score (very poor) and 7 the highest (excellent). The respondents are instructed to pick the number that applies best to them. The raw scores from the responses are calculated and then transformed to a scale of 0-100 points according to instructions from the EORTC scoring manual (111). A higher score on the global QOL scale and functional scales indicates better function while on a symptom scale or single item a higher score means worse symptoms.

There are two important considerations in the interpretation of HRQOL scores. Firstly, the QOL of patients with oesophageal cancer after diagnosis but before start of treatment are often used as baseline for comparison. However, these measurements may be suitable for adjustment of differences between groups in statistical analysis but do not mirror the QOL before the onset of the disease since at time of diagnosis patients may already be influenced by the presence of the tumour and related distress from symptoms. Data based on large random samples from the general population can be used to obtain normative scores to

overcome this limitation. Secondly, not every change in HRQOL can be perceived as clinically meaningful. The differences in mean scores may be statistically significant when the sample is large (172). However, these differences may not be equivalent with what is perceived to be meaningful for the patients. The interpretation of the differences in HRQOL scores should thus be conceived based on what is a clinically important difference for patients (173). Therefore two principle approaches have been advocated to address clinically meaningful differences in scores, the distribution based and anchor-based approach (172). The distribution-based approach may have the same limitations as statistical significance as they are subject to the effect of sample size. Based on the anchor-based approach, Osaba et al suggested that on a scale of 0-100 a threshold of a change of 5-10 scores as little; 10-20 as moderate and greater than 20 as large differences in the clinical interpretation of scores (173). King et al reported a change of 10 points in HRQOL may indicate a reduction in symptoms in a clinical setting based on different clinical groups of patients (174). A review by Cocks et al reported that despite the existence of guidelines, they were not utilized, thus in turn HRQOL results seldom influence clinical practice (175). Thus Evidence based guidelines were proposed by Cocks et al based on a meta-analytic approach and blinded expert opinions to suggest clinically relevant changes (167). These newer estimates are robust in providing guidelines for each QLQ-C30 subscale for sample size calculations and for interpreting the differences between groups as trivial/small/medium/large. The cross-sectional guidelines were used to interpret clinically meaningful differences in HRQOL outcomes from EORTC QLQ-C30 in **Studies I-III** in this thesis. Subsequently, additional guidelines for interpretation of changes over time for longitudinal models were also proposed by Cocks et al (166) and were used in **Study I** in this thesis for interpreting changes in HRQOL scores over time. For example, cut-off mean difference (MD) values for the global QOL scale according to the cross-sectional guidelines are: trivial, 0–4; small, 4–10; medium, 10–15; and large, more than 15. Cut-offs according to the longitudinal guidelines are: trivial, –5 to 5; small, –10 to –5; medium, –16 to –10; and large, less than –16. Moreover, the summary score was the primary outcome in **Study III** is calculated as the mean of 13 out of the 15 EORTC QLQ-C30 scale scales combined (excluding financial difficulties and global QOL) and suggested as a robust single factor model for the QLQ-C30 (176).

10.2 FINDINGS AND EXPLANATIONS

10.2.1 Study I

The main findings in **Study I** were that eating difficulties, irrespective of weight loss, adversely influenced long-term postoperative HRQOL in oesophageal cancer survivors. A vast majority of the HRQOL scales worsened to a level of medium or large clinical significance among those with eating difficulties, independent of weight loss at 6 months, 3, 5 and 10 years after surgery. These results suggest patients with higher problems with eating particularly pertaining to enjoying a meal, sudden feeling of fullness, eating in front of others and problem with taste are identified as a vulnerable group in need of heightened health care support and intervention in order to improve their HRQOL. The reason behind these findings may be explained by the extensive changes in anatomy following surgery for oesophageal cancer. The stomach plays a core function in digestion of food. The four key components of gastric digestive function are its function as a reservoir, acid secretion, enzyme secretion and its role in gastrointestinal motility. Oesophagectomy for malignancy involves removal of the main part of the oesophagus and the upper part of the stomach, and two-field lymph-node dissection, followed by reconstruction using a gastric tube formed from the remaining stomach tissue, which is pulled up into the chest or the neck (88). The permanent anatomical changes with the missing reservoir function of the stomach are often associated with adverse gastrointestinal effects manifesting as eating difficulties. In the postoperative period, patients decline in their physical, role and social function, moreover experience symptoms of fatigue, nausea and vomiting, dyspnea, diarrhea, dry mouth, taste problems and coughing (15). As long as 10 years after the operation, global quality of life, role function and social function deteriorated and symptoms of reflux, eating difficulties, diarrhoea and appetite loss worsened (22). In interview studies, patients have expressed feelings of being embarrassed or stigmatized by constant nausea, diarrhea and choking when eating (177). This might lead to a refrainment in social eating, both in public and at home. The struggle patients undergo has been described as a process of remapping their body and having to learn to eat again (177). This adaptation process incapacitates role, social, emotional functioning and overall HRQOL. Experiencing symptoms and adaptation in eating habits to cope with the symptoms thus have significant impact on many aspects of HRQOL.

10.2.2 Study II

The main results of **Study II** indicated that presence of more symptoms impacting nutrition, affected global QOL, social and physical function at 6 months after oesophagectomy, no matter the level of preoperative BMI or postoperative weight loss. The presence of more NIS

was associated with lower survival in those with high preoperative BMI experiencing major postoperative weight loss. These results highlight the importance of recognizing early on patients with higher NIS as an at-risk group for lower HRQOL who need more support from health care and targeted interventions. Additionally, the results highlight the need to give more attention to those who are overweight and obese before surgery and develop NIS and weight loss after surgery. The anatomical changes from the surgery and the missing reservoir function of the stomach are likely attributable to the collective impact symptoms affecting nutrition. The lower survival among those who were overweight/obese before surgery is probably owing to NIS and weight loss being compounded by underlying sarcopenia and more co-morbidities. This might be a group that are overlooked if preoperative screening for malnutrition is by means of BMI alone. Moreover, most patients themselves consider the weight loss as a positive trait but on the other hand maybe negative due to muscle loss rather than fat. Both sarcopenia and more co-morbidities are recognized determinants of survival and can be worsened with the presence of NIS that impacts HRQOL (178, 179). Screening for sarcopenia in addition to BMI especially in those who are overweight/obese is thereby warranted for.

10.2.3 Study III

The main findings of **Study III** were that the presence of symptoms of both early and late dumping syndrome was associated with poorer HRQOL compared to no symptoms of dumping syndrome. However, even though a small number of patients experience late dumping, its effects were more debilitating on HRQOL than early dumping. These results point to the underlying need to consider dumping syndrome as a clinical complication following oesophagectomy that is objectively diagnosed and managed as recommended.

The gastric pylorus is typically innervated by the vagus nerve, with parasympathetic activity stimulating gastric peristalsis and pyloric sphincter relaxation. During proximal oesophageal transection, a vagotomy is performed, which denervates the gastric conduit. The denervation may lead to clinically noticeable delayed gastric emptying owing to increased gastric wall tension (180, 181). Delayed gastric emptying also contributes to aspiration and respiratory infection and increases anastomotic leakage (182). Intra operative techniques such as pyloroplasty or pyloromyotomy are performed to reduce delayed gastric emptying. Increasingly, intrapyloric botulinum injection with or without digital dilation has also been used to address the issue with delayed gastric emptying (183). However, these techniques have demonstrated no favorable reduction of delayed gastric emptying compared to no

treatment at all and reported to increase dumping syndrome and bile reflux (158, 184). The vagotomy is by itself may also be associated with increase in dumping syndrome especially early dumping due to lack of vagal reflexes (158). The presence of symptoms of early and late dumping and their association with reduced HRQOL can be explained by eating becoming a burden and unpleasant experience because of the dumping-related symptoms. The symptoms can be emotionally distressing, leading to anxiety and apprehension (157). Neuroglycopenic symptoms such as difficulty concentrating, and confusion induced by the reactive hypoglycemia are likely to restrict cognitive function (157). The distressing symptoms are thus likely to interfere with everyday role function. The neuroglycopenic symptoms such as fatigue, weakness, confusion, tachycardia distinct to late dumping symptoms may have a far worse impact on patients' HRQOL as indicated by the results. Moreover, it is also unclear if patients are adequately informed from health care of what dumping syndrome and thereby do not know what to anticipate.

10.2.4 Study IV

In **Study IV** patient's nutritional status at one year after surgery for oesophageal cancer did not differ with respect to whether preoperative dietitian support was received in addition to postoperative support and the level of patient's satisfaction of the support from dietitians. These results emphasize the importance of the role of preoperative dietitian support in addition to the postoperative support in obtaining a nutritional status equivalent (although not higher) to those who get postoperative support alone. It is strongly recommended that nutritional assessment should be undertaken in all patients with an aim of detecting and optimizing nutritional status before surgery (185). Weight stabilization might be thus an appropriate goal of a nutritional intervention in patients who are screened with malnutrition before surgery with the goal of improving survival (185). The possible explanation for similar nutritional status in those with preoperative and postoperative dietitian support as those with postoperative support alone, is a possible catch up effect in terms of weight status. Patients who faced more weight loss before surgery with the provision of adequate support attained a nutrition status similar to those who needed postoperative dietitian support alone. This in turn reflects a good preoperative screening for malnutrition and quality of the support provided. Dietitian contact is considered an imperative step in achieving behavior modification to manage NIS before and after surgery. Patient level of satisfaction is a good indicator of behavior modification, an important goal to manage NIS in patients who undergo surgery for oesophageal cancer (13, 14). In the early postoperative phase, enteral feeding may be provided to improve nutritional status, as well as both mental and physical aspects of quality

of life, but enteral feeding does not completely address the physical and psychological barriers of eating normally (186). However, there was no differences in nutritional status based on the patient's level of satisfaction of dietitian support. It cannot be excluded that there may be other factors, not included in this study, that explain the non-difference in nutritional status.

10.3 CLINICAL IMPLICATIONS AND FUTURE RESEARCH

Patients who have undergone surgery for oesophageal cancer who have NIS need deeper evaluation and intervention to help with the adaptation and thereby improve HRQOL. The goal of the evaluation should be screening for NIS followed by deeper evaluation of the symptoms to diagnose conditions associated with the cause of NIS. Besides dumping syndrome focused on **Study III** of this thesis, there are several other conditions that are indicated as causes for malabsorption and malnutrition after oesophagectomy that contribute to NIS and eating difficulties. The mechanisms behind are likely complex and multifactorial (187). Vagotomy results in delayed gastric emptying that has been discussed above. Moreover, after vagal denervation, exocrine pancreatic insufficiency as a consequence of loss of endogenous neuroendocrine signals which stimulate the pancreas to release digestive enzymes (188). Similarly, bile acid malabsorption may result from both vagotomy and disruption of the enterohepatic circulation of bile acids (189). Small intestinal bacterial overgrowth reflects an altered gut microbiome because of reduced gastric acid secretion, anatomical alterations of the gut, and compromised intestinal motility (187, 190). Furthermore, shifts in the levels of the peptide hormone ghrelin are another biological mechanism that might trigger severe weight loss after surgery for oesophageal cancer (191, 192). Ghrelin is secreted by the fundic glands of the stomach and has a role in appetite signaling to the hypothalamus in a negative feedback loop in relation to weight and the adipocytokine, leptin (40). Ghrelin thereby enhances appetite and increases food intake. It is postulated that the amount of circulating ghrelin is proportional to the amount of residual stomach after oesophagectomy thus causing weight loss (191). Thus, weight loss corresponding to malnutrition, eating difficulties or NIS may result from multifactorial pathophysiological changes in the anatomy after oesophagectomy. EORTC QLQ-OES18 (116) and PG-SGA Short form (150) used in **Studies II and IV** are valid and useful tools for screening for NIS in clinics. However, symptoms specific to dumping syndrome and other conditions contributing to NIS and in turn to malabsorption such as delayed gastric emptying, exocrine pancreatic insufficiency, bile acid malabsorption and small intestinal bacterial overgrowth are not encompassed in the above questionnaires. There is a need for the use of

additional questionnaires such as dumping specific questionnaires as the one used in **Study III** of this thesis in order to differentiate between early and late dumping that has to be extensively validated. Moreover malabsorption associated symptoms may be assessed with the use of validated questionnaires such as the Gastrointestinal Symptom Rating Scale (193). Objective tests such as low ferritin levels ($FE^{-1} < 200$ μg/g) are indicative of exocrine pancreatic insufficiency and positive hydrogen breath test for small intestinal bacterial overgrowth (187). Future research should thus ideally employ a combination of specific questionnaires and objective measures. Dumping syndrome and other possible underlying conditions causing NIS including delayed gastric emptying, exocrine pancreatic insufficiency, bile acid malabsorption and small intestinal bacterial overgrowth and small intestinal bacterial overgrowth are modifiable factors impacting malabsorption. If identified, these are treatable with various interventions. The recommended first line of management for dumping syndrome is with dietary modifications, the secondary stage with acarbose and somatostatin analogues and third line of management with surgical interventions (157). Exocrine pancreatic insufficiency is correctable with pancreatic enzyme replacement therapy (188), bile acid malabsorption with colesevelam (194) and small intestine bacterial overgrowth with antibiotics (195). Targeted interventions addressing these conditions together with behaviors modification with eating in the future may be a key step to reducing impact from the symptoms.

There are likely surgically modifiable risk factors for NIS that need further exploration in the future. No additional benefit from operative procedures or botulinum treatment for delayed gastric emptying has been indicated. Hence, no treatment of the pylorus is recommended (184). It is proposed that new migrating motor complexes develop within the gastric conduit soon after surgery, restoring gastric contractility and normal pyloric tone (184). Moreover, although several operative techniques including open 2- or 3-stage resection and minimally invasive approaches exist, the transection of the vagi is a routine part of the oncological resection, irrespective of operative technique. In this context, a vagal sparing oesophagectomy has been suggested as a physiologically better approach with favourable outcomes for delayed gastric emptying and dumping symptoms however remains to be validated (196). Moreover, the use of a narrow gastric conduit rather than the whole stomach is considered favourable for delayed gastric emptying (197).

11 CONCLUSIONS

The main aim of this thesis was to contribute to clinical decision making regarding which nutritional factors influence HRQOL and survival after oesophageal cancer surgery and identify factors associated with improved nutritional status. The main aim was achieved as the findings of **Studies I-III** were in line with the hypothesis. **Studies I-III** in this thesis has identified eating difficulties, NIS and symptoms of dumping syndrome as risk factors for deterioration of HRQOL after surgery for oesophageal cancer, thereby identifying patients who have an underlying need for support to improve their HRQOL. Although factors improving nutritional status could not be achieved in **Study IV** there was indication for effective preoperative screening and support from dietitians to achieve weight stabilization and lower NIS postoperatively although not improved nutritional status. The main conclusions of this thesis are,

- Eating difficulties, whether accompanied by clinically significant weight loss or not, are adverse determinants of all aspects of HRQOL throughout the postoperative period up to 10 years after surgery.
- NIS adversely impact global QOL, physical function and social function at six months after surgery irrespective of the degree of preoperative BMI or postoperative weight loss.
- The presence of severe NIS is associated with poorer survival in those with high preoperative BMI experiencing major postoperative weight loss.
- Symptoms of early and late dumping syndrome have a negative influence on certain HRQOL outcomes at one and half years after surgery. Late dumping had a worse effect on HRQOL than early dumping.
- Dietitian support initiated preoperatively and a high level of satisfaction of the dietitian support were not associated with an improved nutritional status at one year following surgery for oesophageal cancer.
- The similarity in nutritional status between patients in whom dietitian support was initiated pre and postoperatively may reflect effective screening of malnutrition and dietitian support in centres for treatment of oesophageal cancer in Sweden.

12 POPULÄRVETENSKAPLIG SAMMANFATTNING

12.1 BAKGRUND

Matstrupscancer är en besvärlig cancertyp som drabbar cirka 400-500 personer i Sverige årligen. Globalt är cancerformen den 11:e vanligaste cancerformen och den 6:e vanligaste anledningen till cancerdöd. Matstrupscancer delas huvudsakligen in i två typer, adenocarcinoma och skivepitelcancer. De vanligaste riskfaktorerna för adenocarcinoma är halsbränna och övervikt medan alkohol och rökning ökar risken för skivepitelcancer. Eftersom tumörer i matstrupen kan växa sig stora utan några märkbara symptom är det många patienter som söker läkare i ett sent skede av sjukdomen. De första vanligaste symptomen är tilltagande svårigheter att svälja, så kallad dysfagi, smärtor i samband med matintag och viktnedgång. Behandling i botande syfte innebär omfattande kirurgi som kombineras med cellgiftsbehandling. Kirurgi innebär oftast att hela matstrupen och/eller delar av magsäcken tas bort och att det bortopererade området ersätts med en bit av magsäcken. Operationen är sto och omfattande vilket ökar risken för komplikationer i efterförloppet och nedsatt livskvalitet på både kort och lång sikt (upp till 10 år) efter operationen. Viktnedgång är ett problem som drabbar patienter med matstrupscancer såväl före som efter operationen. Var femte patient som opererats förlorar minst 20 % av sin vikt efter kirurgi, mätt 6 månader efter operationen. Ätsvårigheter, aptitlöshet och smärtor vid måltid angavs vara ett stort problem hos dem som förlorat mest i vikt. Det övergripande syftet med denna avhandling var att kartlägga nutritionsfaktorer som långsiktigt påverkar livskvalitet och överlevnad, och finna faktorer som minskar risken för viktnedgång och ger bättre nutritionsstatus efter operationen för matstrupscancer.

12.2 METODER OCH RESULTAT

12.2.1 Studie I.

Syftet med **Studie I** var att undersöka om ätsvårigheter tillsammans med viktnedgång påverkar livskvalitet hos patienter upp till 10 år efter operation för matstrupscancer. Studien byggde på det Svenska esofagus och cardiacancerregistret (SECC) vilket omfattar alla patienter som opererats för cancer i matstrupen i Sverige under april 2001 till och med december 2005 med långtidsuppföljning (kohortstudie) upp till 10 år efter operationen. Medicinska journaler granskades och information om patienten, tumören och operationen insamlades i samband med diagnos och behandling. Sex månader, tre, fem och 10 år efter operation fick patienterna besvara en studiespecifik enkät om vikt samt validerade enkäterna om livskvalitet och olika symptom vid dessa tillfällen. Analyserna justerades för viktiga storfaktorer. Huvudresultat var att patienter som upplevde mer ätsvårigheter med eller utan stor viktförlust försämrades påtagligt avseende global livskvalitet, funktioner och symptom på lång sikt över tid.

12.2.2 Studie II.

Studie II belyste om symptom som påverkar nutrition och viktminskning förklarar sämre livskvalitet sex månader efter operation för matstrupscancer och om dessa faktorer påverkar överlevnad. Studien baserades på samma datakälla som i **Studie I**. Analyserna justerades för viktiga storfaktorer. Analyserna tog hänsyn till övervikt och normalt body mass index (BMI) innan kirurgi påverkade resultatet. Studiens huvudresultat var att patienter som rapporterade mer symptom som påverkar nutrition hade betydligt sämre livskvalitet än de som rapporterade mindre av sådana symptom. Resultaten var oberoende av viktminskning och BMI innan operation. Överviktiga patienter som rapporterade mer symptom som påverkar nutrition och viktminskning efter kirurgi hade ökad risk för dödlighet på lång sikt jämfört med patienter som hade mindre problem med dessa symptom.

12.2.3 Studie III

Studie III undersökte om symptom av dumping syndrom efter operation för matstrupscancer påverkar livskvalitet. Symptom av dumping kan upplevas i samband med matintag då passerar maten för snabbt från magsäcken till tarmen. När symptom uppkommer inom en timme efter måltid kallas detta tidigt dumping medan om de uppkommer efter två – tre timmar efter måltid kallas det sen dumping. Studien baserades på en nationell svensk kohortstudie kallad OSCAR studien som inkluderade patienter som genomgått operation för matstrupscancer i Sverige under januari 2013 till december 2016 med uppföljning till ett och halv år efter kirurgin. Kliniska data om sjukdomen och behandlingen inhämtades från patienternas medicinska journaler. Huvudresultat visade att patienter som rapporterade symptom på tidigt och sen dumping hade sämre livskvalitet jämfört med de som inte upplevde några dumping symptom. De patienter som rapporterade sen dumping hade sämre livskvalitet än de som rapporterade tidig dumping.

12.2.4 Studie IV

Studie IV undersökte om dietiststöd innan kirurgi och patienternas upplevelse av stödet från dietisten påverkade patientens nutritionsstatus efter operation. Studien baserades på samma datakälla som i **Studie III**. Information om dietiststöd och patienternas upplevelse av stödet inhämtades genom en studiespecifik enkät. Nutritionsstatus avsåg viktminskning efter kirurgi och patientrapporterade symptom som påverkar nutrition. Studien visade att dietiststödet inte påverkade patientens nutritionsstatus oavsett om patienten fått dietistkontakt innan och efter kirurgi jämfört med endast efter kirurgi. Upplevelsen av stödet från dietisten var inte heller relaterat med bättre nutritionsstatus efter operationen. Resultat reflekterar effektiv nutritionsbedömning innan kirurgi i vid kliniker i Sverige som behandlar patienter med matstrupscancer och även att stödet från dietisterna är mycket tillfredsställelse.

12.3 SLUTSATSER

Sammanfattningsvis så visar denna avhandling att symptom som påverkar nutrition och ätsvårigheter efter kirurgi för matstrupscancer är viktiga prediktorer för försämrad livskvalitet och överlevnad. Patienter som upplever symptom på dumping syndrom har en sämre livskvalitet och behöver uppmärksammas. Dietistkontakt är ett viktigt stöd för patienter både före och efter operation för matstrupscancer för att upprätthålla ett gott nutritionsstatus.

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